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CLINIC OF DRS. RALPH PEMBERTON
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INTRODUCTION TO THE PROBLEM OF RHEUMATOID
DISEASE: CLASSIFICATION, ETIOLOGY AND DIAG-
NOSIS

THE PROBLEM OF RHEUMATOID DISEASE

Incidence.—Rheumatoid diseases present serious problems both socially and medically. The prevalence of rheumatoid diseases and the economic cost occasioned by them are not widely recognized. The data presented by the survey conducted by the United States Department of Public Health regarding the incidence of various chronic diseases in the U.S.A., revealing that this group of diseases afflicts 6,800,000 persons, or approximately one out of every nineteen persons in the entire population yearly—a number greater than that involving any other group of chronic disease—will come as a surprise to many. Of these, 147,000 are regarded as *permanently* invalided. These disturbances of the locomotor system affect not only a greater number of persons than more widely appreciated chronic diseases such as arteriosclerosis, tuberculosis and diabetes, but are also responsible for a greater total loss of days of productive work than are any of the latter. *It is estimated that rheumatic disorders are responsible for the loss of 97,000,000 days of work annually.* One of the many popular misconceptions regarding rheumatism is that rheumatic diseases constitute a problem of later life only. However, the same survey reveals that more than 50 per cent of disability inci-

dental to rheumatism is found among persons *under forty-five years of age*.

ECONOMIC SIGNIFICANCE.—The significance of these several factors in terms of national economy cannot be overestimated. By a simple calculation it means that an equivalent of over 320,000 otherwise able persons in the United States *are rendered unemployable for an entire year by these disorders*. Thus the total loss of "man power" presents a challenge quite apart from the factor of human suffering occasioned by the disease. An enforced "layoff" of this number of persons would instantly enlist the attention and study of those seriously concerned with national economy. While the medical aspects constitute our present major concern, it should be pointed out in passing that the greatest incidence of these disorders occurs among persons subjected to the conditions imposed by sub-maintenance incomes; namely, among families receiving less than \$1000 annually. What factors are involved in the large incidence among this group, whether inadequate nutrition or exposure from poor housing, are not yet evident. It should be added, lest improper conclusions be reached, that the disorders do occur with lesser frequency but with no less violence among the more fortunate economic classes, wherein the chances for better hygiene, housing and nutrition are available.

BIOLOGICAL CONSIDERATIONS.—Certain broad biological considerations throw additional light upon the magnitude and nature of the problem presented by these diseases. The rheumatic diseases have a *very long history* and *wide distribution* in nature. Recognition of this has practical importance because it suggests at once the inadequacy of narrow biological concepts sometimes advanced by certain self-styled authorities as to supposed causes, and the consequent exploitation of uncritical treatment based upon these alleged factors. The skeletal remains of prehistoric men show that rheumatic diseases were among the hazards of the earliest forms of human life. Even before the advent of man the great dinosaurs had arthritis. The disease left its record in vertebrae joined together by processes similar to those seen today taking place in both domestic and wild animals. A recent survey of arthritis among wild animals shows that rheumatism may develop *not only* when animals live in captivity, but also in their native habitat. The disease develops in both carnivorous and herbivorous animals, and this fact holds little comfort for either the exclusive "meat eater" or the vegetarian who expects his extreme dietary habits to protect him from rheumatism. Again it should be

emphasized, as it was with respect to environmental conditions, that arthritic disorders are not to be accounted for by superficial considerations, but must be studied from a comprehensive *biological* and *physiological* point of view.

CLASSIFICATION

Rheumatic diseases, while showing various features in common, are by no means all alike. The first step in an adequate appraisal of a given condition and the institution of adequate therapy is therefore *proper classification* and *diagnosis*.

In contrast to some other clinical condition this matter is relatively complicated. The reasons for this are to be found in the fact that the tissues of the locomotor system have but a few types of reactions to various kinds of agents and agencies, and in the further fact that once a pathologic process is started in these tissues, subsequent development of the lesions often follows a common pattern. These facts, in view of the usual circumstances under which the physician first sees the case, *i. e.*, long after the beginning, makes it necessary to employ a *descriptive* kind of classification rather than one based primarily upon *etiology*. This necessity need not be regarded as discouraging, however, inasmuch as effective measures of therapy are readily available, except in a few instances as will be noted later.

The True Arthritides.—The true arthritides, *i. e.*, those in which the articular structures are the site of marked pathologic processes, are divided into two main types: (1) *atrophic* (rheumatoid or proliferative arthritis) and (2) *hypertrophic* (osteo-arthritis or degenerative arthritis). A significant number of patients present a combination of the features of atrophic and hypertrophic arthritis which is classed as *mixed arthritis*.

Other classes of lesser quantitative significance include septic varieties, *e. g.*, *gonococcal*, *pneumococcal*, *staphylococcal*, *streptococcal*, *tuberculous*, *traumatic*, *gouty*, *chemical* (in the restricted sense, *e. g.*, lead poisoning), *scorbutic*, *hemophilic*, and *neurogenic*. These latter varieties present evidence of an obvious etiology whereas the former, atrophic and hypertrophic arthritis, are related to no single specific etiologic factor but are frequently associated with certain precipitating factors, to be discussed later, which, for practical purposes, may be regarded as etiologic. Other clinical conditions, often marked by extreme disability but associated with lesser degrees of intra-articular involvement, include *rheumatic fever*, *fibrositis*

(i. e., *muscular rheumatism*), *menopausal arthralgia*, and the recently described "*hit and run*" *arthritis*.

Other Syndromes Associated with Locomotor Disability.—Other clinical syndromes occasionally associated with disability in the locomotor system include *beri-beri*, *rickets*, *Raynaud's disease*, *scleroderma*, *erythromelalgia*, *peripheral neuritis*, *diabetes*, *hypothyroidism* and *primary anemia*. These conditions usually present no diagnostic difficulties, but the articular manifestations may become so prominent as to be the *first symptom* to direct attention to the presence of the underlying condition.

A number of *infectious diseases* are also occasionally marked by disturbances in the locomotor system of greater or lesser significance. While some of these may resemble superficially acute stages of atrophic arthritis, there are adequate and obvious means of recognizing the underlying factors. The more serious of these sometimes producing permanent articular damage include *syphilis*, *typhoid fever*, *dysentery*, *leprosy*, *undulant fever* and *meningitis*.

The general toxic influence of these and other infectious states too numerous to enumerate here may at times be characterized by transient joint pain and disability. Typical of this latter kind of involvement is that associated with *influenza*. Therapeutic attention in all of these conditions should be directed toward the correction of the major aspects of the syndrome and not to the articular manifestation alone.

Table 1 illustrates in outline a general descriptive classification of diseases involving the locomotor system based upon the principal clinical and clinicopathologic features characterizing each syndrome, together with the most frequently cited actual or probable etiologic factors.

ETIOLOGY AND DIAGNOSIS

Atrophic Arthritis.—Atrophic arthritis is a systemic disease characterized in the later stages by "atrophic" or wasting manifestations in the *skeletal* and *muscular systems*, coupled with evidence of *dysfunction of other tissues*. This condition appears most frequently among persons in the third to the fifth decade, and more often in women than in men. While the former features in the locomotor system often predominate and provide the basis for the chief complaints of the patients, the latter disorders are of equal or even greater significance and require attention in any satisfactory therapeutic regimen. The *systemic manifestations* include at least functional exhaustion,

TABLE 1

SIMPLIFIED CLASSIFICATION OF RHEUMATIC DISEASES BASED UPON PREDOMINANT CLINICAL SYMPTOMS

Class.	Features.	Etiologic and precipitating factors.
Atrophic arthritis. (Rheumatoid) Proliferative)	Severe systemic reactions. Skeletal, muscular atrophy. Proliferation of synovialis. Intra-articular pathology. Polyarticular distribution.	Unknown. Infection. Fatigue. Exposure. Trauma—physical and psychic. Metabolic. Gastro-intestinal dysfunction.
Hypertrophic arthritis. (Osteo-arthritis) (Degenerative)	Moderate systemic reactions. Overgrowth of articular margins. Degeneration of cartilage. Intra-articular pathology. Occasionally mono-articular distribution.	Unknown. Cumulative effects of traumata, toxemia. Nutritive and vascular deficiencies. Infection. Gastro-intestinal dysfunction.
Mixed arthritis.	Combination of atrophic and hypertrophic.	As above.
Fibrositis. (Muscular rheumatism)	Moderate systemic reactions. Inflammation of muscles and tendons. Extra-articular.	Unknown. Infection. Toxemia. Trauma.
Gout.	Systemic reactions. Deposits of sodium urate or tophi. Intra-extra-articular.	Unknown. Exposure. Fatigue.
Rheumatic fever.	Marked systemic reactions. Fever, cardiac involvement. General toxemia. Connective tissue pathology. Peri-articular. Polyarticular distribution.	Unknown. Virus. Streptococcus haemolyticus. Nutritive defect: Vitamin C.
Septic arthritis.	Purulent exudation. Intra-articular. Generally localized.	Infection. Direct or metastatic with gonococcus. Streptococcus haemolyticus, pneumococcus, staphylococcus, B. typhosus.
Traumatic arthritis.	Local. Overgrowth degenerative.	Injury.
Tuberculous arthritis.	Systemic reactions. "White swelling," tubercle formation. Often mono-articular.	Infection with Koch's bacillus.
Neurogenic arthritis. (Charcot) (Syringomyelia)	Systemic reactions. Combination of atrophic and hypertrophic pathology.	Syphilis. Nervous system. Hemorrhagic degeneration of cord.
Miscellaneous varieties.	Post-infectious. Chemical. Scorbutic. Hemophilic. Generally polyarticular.	Infectious diseases. Lead poisoning. Vitamin C deficiency.

anemia, fatigue, disturbances in the nervous system, dysfunction of the gastro-intestinal tract, and often a toxic involvement of the liver. These factors will receive further emphasis in connection with the discussion of therapy.

Among the tissues of the body reflecting a response to some undefined stimulating factor or factors is the *synovial membrane* or *synovialis* which undergoes proliferation, with a resultant pannus formation extending over the cartilage with obliteration and destruction of the latter. The sequence of changes is often associated with periods of swelling of the joint capsule due to a sterile effusion. In addition to this, the peri-articular tissues may be hyperemic and present a reddened and feverish aspect. This stage is often accompanied by *marked tenderness* and *pain*. The result of these processes is that the joint loses its substance and presents in the peripheral joints a sunken and wasted appearance. The associated muscular wasting serves to exaggerate the loss of tissue. A somewhat atypical, and fortunately less common variety of atrophic arthritis involving the spine and known as *spondylitis rhizomélisque*, occurs more often among men than women. The systemic manifestation may be particularly severe and the condition is characterized in the later stages by ankylosis of the pelvic and shoulder girdles together with calcification of the anterior common ligament of the spine.

These articular manifestations may follow an *intermittent* or somewhat *continuous course*, with severe pain and discomfort and disability. Several joints are usually involved, and *symmetrical* distribution is the rule. *Mild fever, leukocytosis, secondary anemia*, and an *increased sedimentation rate* are usually present during the period of active inflammation in the joint. Activity and use of the joints usually serves to *aggravate* all of these symptoms.

The *secondary effects* and *sequelae* of the articular disturbances often assume major proportions: The lowered morale, the irritated nervous system, and the residual disability from the joint lesions in the patient who has suffered from the disease for an extended period of time, constitute an important aspect of the medical problem presented to the physician. At this stage a detailed knowledge of the underlying pathologic mechanism of the articular lesions seems of slight importance. Even a knowledge of etiologic factors, if recognized with certainty, could not be applied with any conspicuous success at this stage of the problem. Etiologic factors are those which set in motion a pathologic process; they do not, even in the simplest cases, define and determine the *entire sequence of events* in the individual. *Continuously acting factors* which unfavorably influence the course of events assume thereby the importance usually attributed to etiologic factors. This prin-

ciple is of great therapeutic significance and has been widely overlooked.

ETIOLOGIC CONSIDERATIONS.—While it has long been generally assumed that *infectious factors* play a predominant rôle in atrophic arthritis, recent studies indicate that the identity of a specific factor, if present, remains undetermined. Thus the once suspected *Streptococcus viridans* has been acquitted on the basis of testimony presented by Angevine and Cecil, who formerly held the opposite tenet. The *Streptococcus haemolyticus*, long incriminated on circumstantial evidence, has likewise been released as a directly acting factor for lack of evidence. The virus-like particles isolated from tissues and exudates of arthritics by Schlesinger and others have not been shown to possess the capacity to induce articular disease. The pleuro-pneumonia-like organism first charged by Sabin and later by Swift and Brown as the primary causative factor of atrophic arthritis and rheumatic fever has been found by these workers with the same frequency in both normal and pathologic tissues. In light of these observations it would appear that *no specific agent* capable of identification by means now available for direct examination or growth on culture media is uniformly found among arthritics. Only indirect circumstantial evidence then remains to incriminate infectious factors. The antibodies found in the sera of patients which react with bacteria as agglutinins, with chemical fractions of them as precipitins, or as enzymatic agents such as fibrinolysins, are not to be dismissed from consideration, but their etiologic importance must be interpreted conservatively as nonspecific until more direct evidence is at hand regarding their significance. The tissue reactions of atrophic arthritis, *viz.*, inflammation, round cell infiltration and the systemic responses (fever, leukocytosis and increased sedimentation rate), can also be referred to an infectious though nonspecific type of etiology.

Hypothetical views have been advanced to explain the mechanism whereby infectious factors may play a rôle and yet be missed by the aforementioned studies. The first and simplest is that micro-organisms are *transient* invaders into the joint tissues and the chance of their isolation either from the blood or the tissues would be slight unless the samples were obtained within the narrow limits of time during which viable organisms were present. The second and somewhat more complicated explanation is based upon the possibility that the articular tissues might be sensitized to the products

of bacterial metabolism at the sites of focal infection *elsewhere* in the body. A third explanation, somewhat more hypothetical and tentatively advanced by the writers, is based upon the view that the *physicochemical integrity* of the articular tissues and the others involved in arthritis can be *undermined* by various means. Accordingly it appears that materials elaborated by micro-organisms at the sites of focal lesions may act directly as noxious agents upon derivatives of the mesoderm, inducing either proliferative or degenerative responses, depending upon the kind of material, its concentration, and the reactivity of the tissue involved. Still another physiologic influence of the materials elaborated by invading micro-organisms depends upon their *antigenic* qualities. As antigens these materials may induce a modification in the serum proteins with an increase in the proportion of serum globulin. As toxic agents these materials may be combined with amino acids or other potential tissue ingredients to produce nontoxic substances which are excreted and thus lost to the economy. These several losses of actual or potential tissue ingredients decrease the amounts of these substances available for the maintenance of the articular structures and so undermine it. From this point of view mechanical wear and tear upon the tissues involved is not an entirely separate kind of factor but an *additional* one, the effect of which would be *cumulative* with the infective, toxic, and nutritive influences.

In view of the systemic nature of many of the symptoms of arthritis together with the generally symmetrical distribution of the articular lesions, it is further conceivable that some of the features of the arthritic syndrome reflect abnormal activities upon the part of certain "*central factors*," either *nervous* or *endocrine*. Among the centrally acting factors which at the moment appear capable of producing the symptoms seen in arthritis is the pituitary. Imbalance of the several hormones elaborated by this organ not only disturbs the normal balance maintained among the other endocrine glands, but also may act directly upon skeletal and other tissues. Overproduction of the growth-promoting factor, for example, may lead to the overgrowth of the articular margins comparable to that occurring in hypertrophic arthritis. This relative overabundance may be secondary to involution of the gonads or to stimulating agents from infection. By the same token, hypo-activity of the pituitary may lead to increased susceptibility to infection, fatigue, anemia and generalized atrophy, conditions common in atrophic arthritis.

Whether these suggestive similarities, which might be further elaborated if space permitted, are sufficient to provide therapeutically important procedures remains to be determined. The practical aspects of this question are discussed in greater detail in another chapter of this symposium. There is no doubt, however, in the minds of the writers that further experimental exploration of this general field in arthritis will be fruitful.

While all of the aforementioned hypotheses are based upon data which are only partially supported by direct lines of evidence, the last mentioned has the practical merit of providing a more or less satisfactory way of interrelating the influence of several different kinds of factors which appear to have clinical importance. Furthermore it shows the necessity of giving therapeutic consideration to *all factors*, chemical and mechanical, which can be brought to bear upon the situation. This aspect of the problem will be considered in fuller and more practical detail in the sections on therapy.

Hypertrophic Arthritis.—Hypertrophic arthritis is a disease characterized in the later stages by *hypertrophic* manifestations in the *skeletal system*, usually coupled with *systemic evidence* of dysfunction in other tissues. It is generally held that the hypertrophic features, particularly in the articular tissues, represent secondary responses to primary degenerative lesions. Inasmuch as this disorder usually appears in the later decades of life, it is regarded as a disease incidental to old age. Similar articular manifestations may appear following traumatic episodes.

In view of these several considerations, it is believed in some quarters that *age* and *trauma* constitute the major etiologic or precipitating factors in this condition. The therapeutic corollary erroneously assumed to follow these observations is that nothing can be done for the care of the patient with hypertrophic arthritis except to advise him that his age has produced the disease, that the joints are not likely to become ankylosed, and that therefore he need not bother with his medical problem. Too frequently the *other disturbances* associated with the articular lesions are overlooked. It is true that full knowledge regarding the factors involved in the processes of degeneration is not yet at hand. However, it is probably fair to assume that, for the lack of a better hypothesis, degenerative processes represent the cumulative effects of noxious agents which are, by and large, essentially similar to those producing acute inflammatory reactions. The differ-

ence between an inflammatory and a degenerative reaction may be attributed to either a lesser concentration of the noxious agent or to differences in the reactivity of the tissues. In any event, it is clear that the pain, tenderness and swelling of the developing Heberden's node represents more than the completely symptomless overgrowth and spur formation that appears to be common to practically all persons who reach the later decades of life and who cannot with reason be classed with those persons who distinctly suffer from clinical hypertrophic arthritis.

THE CONTROL OF ARTHRITIS

It becomes evident from the foregoing considerations that adequate control of both types of arthritis requires a broad approach from several different angles. These include concerted action from the social, individual and academic points of view.

The *social approach* is aimed at a reduction of the general incidence of the disease by means of better housing and nutrition of the poorer classes, by a decrease of the industrial hazards of exposure to cold and damp, and reduction to a minimum of traumatizing factors incidental to work. This further requires provision of proper care for the victims of chronic arthritis as well as for victims of acute diseases, by expansion of existing hospital facilities and convalescent homes through the cooperation of the Department of Public Health. Finally, the social aspect of the program of control requires an expansion of the educational facilities, both lay and professional, regarding the complex nature of these diseases.

The *individual medical attempt at control* requires determination of the tides which characterize the frequently fluctuating symptomatology of the disease, in order to re-establish the state of health. This includes reduction to a minimum of the several individual deficiencies which characterize the syndrome. This sometimes necessitates an adjustment to, or removal from, environmental factors which handicap the patient. A variety of factors may contribute to reduction in the severity of symptomatology, incident to the lesions in the tissues, and diminish the rate of progress of the pathologic changes in afflicted individuals. The full utilization of the benefits to be derived from available influences requires the application of all of the technics of internal medicine, orthopedics and surgery, coupled with the exercise of mature clin-

ical judgment in the coordination and integration of these measures.

The *academic* or *experimental approach* is aimed at a further understanding of the bases of the problem. In broad outline this involves a detailed study of the natural course of the disease, remissions and exacerbations, by means of clinical, biochemical and physiologic technics, and a study of the influence of age, nutrition, infection, the endocrines, and trauma on the joint tissues. It appears appropriate to conduct an exploration for the presence of parasitic forms, viruses, and bacteria in the fixed and fluid tissues of patients during the active stages of the disease. The knowledge of the underlying nature of the changes in the articular tissues would be further illuminated by an extended study of pathologic lesions, particularly during the early period of involvement. Pending a full understanding of the problem, exploration of all newly acquired pharmacologic agents and physical agencies in reference to therapeutic value is justifiable within the limits of reasonable safety. Finally, the correlation of all known factors regarding the disease in the light of contemporary knowledge of cognate fields might be expected to bring to light new relationships of unrecognized therapeutic or prophylactic significance.

It is perhaps needless to add that the campaign against rheumatism must be conducted along a wide front. The campaign can be successful only if waged with intelligence and confidence, founded upon a basic knowledge not only of the ways of rheumatism, but also of the *defensive resources*. The adequate marshalling of the latter, if specifically directed, is generally sufficient to stem the tide of the most devastating aspects of the disease.

The succeeding articles of this symposium are intended to familiarize the reader with the nature of the multiple assault, both from without and from within, made by rheumatic disorders on the human body and the ways and means by which each specific kind of attack can be most effectively controlled.

CLINIC OF DR. EDGAR W. SPACKMAN

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THE ROENTGEN ASPECTS OF CHRONIC ARTHRITIS

THE increasing interest shown by the medical profession in the use of roentgen rays as a diagnostic aid in arthritic conditions indicates the importance of this subject. *x*-Ray examination will not only *differentiate* between the various types of arthritis, but it is a valuable aid in establishing the *degree* of involvement, thereby indicating a favorable or unfavorable prognosis. The interpretation of the *x*-ray evidence should always be correlated with the clinical aspects of the case. In general, however, a joint which shows less involvement to *x*-ray inspection offers a better prognosis, and in most cases a greater degree of usefulness after the attack is over, than one which shows advanced changes. Therefore, in many cases the *x*-ray findings do not parallel the clinical findings and both must be carefully considered in each individual case.

Terminology.—Chronic arthritis, excluding joint changes due to specific etiologic factors such as syphilis, gonorrhea, pyogenic infections, trauma, gout and central nervous disorders, can be divided into two classes, *atrophic* and *hypertrophic*. The *atrophic* variety is also commonly known as "rheumatoid" or "proliferative" arthritis. The *hypertrophic* form is known also as the "degenerative" or "osteo-arthritis."

These terms are somewhat confusing as the term "proliferative" expresses the changes most marked to pathologic examination in which extensive soft tissue proliferation is present in and about the joints. The usual radiographic examination, however, does not visualize the soft tissues and the changes seen on the *x*-ray films are atrophic in nature. "Degenerative" likewise expresses the feature of greatest importance from the standpoint of pathologic examination, but to *x*-ray visualization hypertrophy of the bony structures is the most prominent feature.

We therefore believe that the terms "atrophic" and "hypertrophic" best express the outstanding characteristics of the two varieties of chronic polyarthritis from the standpoint of *x*-ray diagnosis.

Limitations and Possibilities in Roentgenographic Diagnosis.—We must constantly bear in mind that the purpose of the *x-ray* examination is to *interpret* pathologic changes, and in dealing with the image of the lesion on the roentgenogram, strict recognition of the limitations as well as the possibilities of diagnostic procedure should be known. We can demonstrate only those processes which are *sufficiently advanced* to produce a recognizable change in the density and contrast of the tissues as viewed by the *x-ray*.

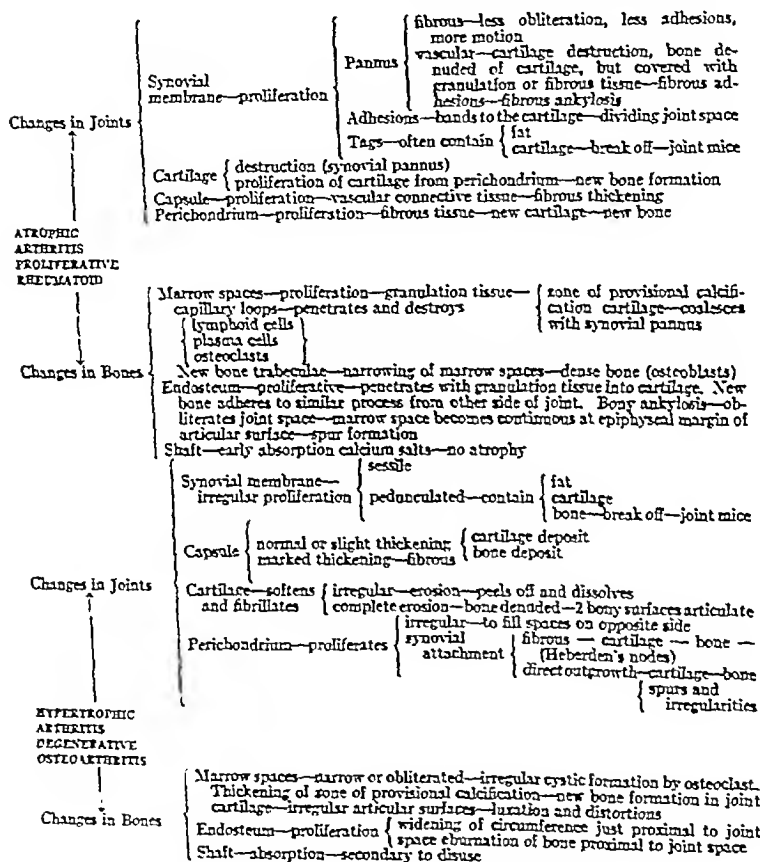
All early and acute signs of arthritis deal with the soft tissue structures, and the only possible identification is by means of exceedingly soft radiation produced at very low voltages. On the usual type of radiographic film, these changes are completely obliterated, and we therefore very strongly recommend when examining those joints in which early changes are suspected, the use of *exceedingly soft radiation* as a *supplement* to the usual standard examination.

Stereoscopic views are of definite advantage in many cases, especially in dealing with the larger joints. We feel, also, that sufficient advantage is not taken of *serial* exposures. Comparative *x-ray* examinations at more or less regular intervals to check the progress of the case is very valuable. Changes as shown on the films do not necessarily parallel the clinical observations and often give considerably more information to the clinician than any single isolated observation.

In considering the *x-ray* evidence, it is best to avoid reading clinical data into the roentgen interpretation, but many workers do not fully realize the importance of giving the radiologist a concise knowledge of the *clinical aspects* of the disease in each particular case. If all phases are not carefully weighed and considered, the result is too often a report from the *x-ray* department which is not only confusing but may be misleading. We therefore wish definitely to emphasize the fact that *x-ray* studies in these conditions are not to be regarded as a *separate* and *isolated* diagnostic procedure, but a very important part of the *complete study* of the case, and they are always to be *correlated* with the clinical and laboratory aspects. Consultation between pathologist, radiologist and clinician is therefore of the greatest importance in this type of work.

Hypertrophic Changes Without Symptoms.—An important group of cases are those showing hypertrophic changes without symptoms. These are almost universally present in older patients, who are regarded as potential arthritics. In-

cluded are most patients past the third decade of life in which one capsular thickening, spur formation, or changes in the calcium distribution about the joint vicinity can be demonstrated. These pathologic changes may have been present for years, but they remain unrecognized until a roentgen examination is requested because some relatively slight trauma



causes pain and distress entirely out of proportion to the exciting agent.

This is a feature of great importance, especially from the *medicolegal* aspect. Radiologists are commonly called to give court testimony in cases where relatively slight trauma has apparently produced severe symptoms, and in many of these cases a previously existing arthritic condition has been potentially present.

Types of Pathologic Change in the Bones and Joints.

—In reviewing the outstanding diagnostic features of arthritis from the standpoint of *x-ray* examination it is well to correlate closely the changes shown on the films with the known pathologic features. We, therefore, submit a brief table of

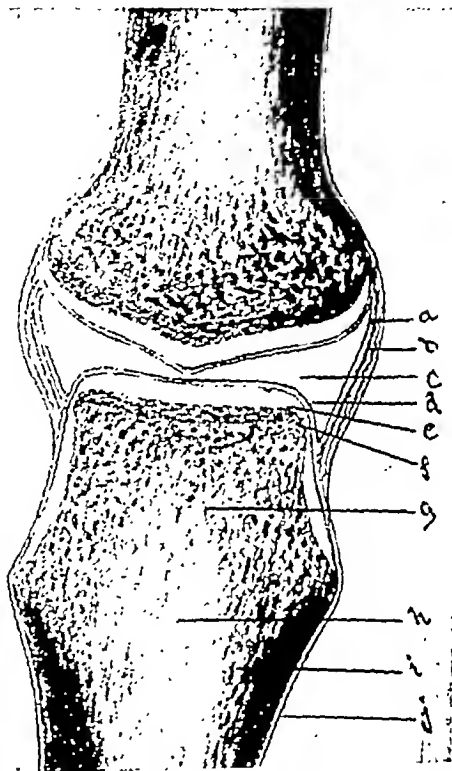


Fig. 181.—Normal joint. Diagram of a simple joint in which two bone ends covered by their cartilage articulate, as in the phalangeal joints: *a*, synovial membrane; *b*, joint capsule; *c*, joint space; *d*, perichondrium; *e*, joint cartilage; *f*, zone of provisional calcification; *g*, spongy bone; *h*, medulla; *i*, cortex; *j*, periosteum. (From author's article in *Amer. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

pathologic changes (page 1605) to clarify the points brought out in the *x-ray* interpretation. The clinician can then follow the line of reasoning and analysis which the radiologist uses in the interpretation of his evidence.

The structures comprising a normal joint are diagrammed

in Fig. 181 as a means of comparison with the illustration and description of the pathologic changes in the two varieties of arthritis under discussion. To show these features on the radiographic illustrations, we have chosen the phalangeal

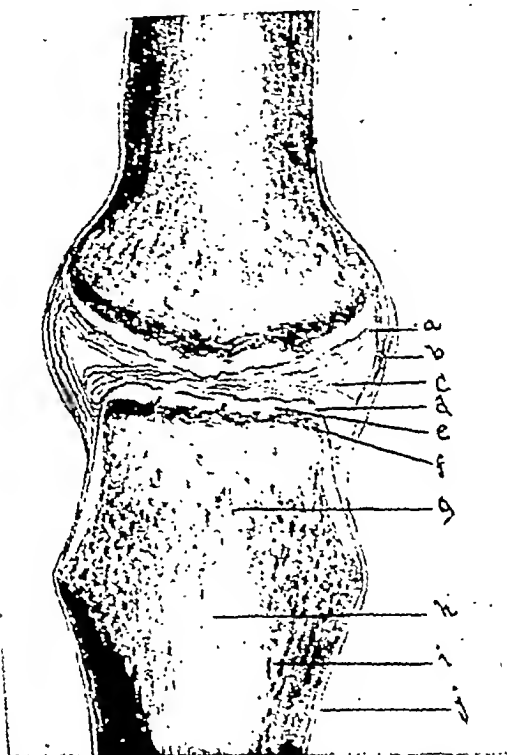


Fig. 182.—Atrophic arthritis—early stage. Diagrammatic illustration of pathologic changes in early atrophic arthritis: *a*, proliferation of synovial membrane to form a pannus; *b*, thickening of joint capsule; *c*, joint space partially filled by ingrowth of pannus; *d*, irregular destruction and proliferation of perichondrium; *e*, erosion of cartilage by the synovial pannus; *f*, irregularity of line of provisional calcification due to ingrowth of capillary loops; *g*, atrophy of spongy bone; *h*, *i*, *j*, unchanged. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

joints, the pathologic features being more simple and characteristic as a rule in the smaller joints than in the larger and more involved articulations.

Atrophic Arthritis.—In atrophic arthritis, the *earliest recognizable stage*, from the x-ray standpoint, is merely a

slight increase in the width of the joint space; this is due to an excess of fluid and a tendency to bulging of the capsule and slight thickening of the periarticular tissues. It may sometimes be recognized on the soft tissue type of radiographs above described. The synovial membrane thickens and forms granulations which gradually spread over the cartilage surfaces of the joint, producing the so-called pannus. The perichondrium reacts to form irregular areas of new cartilage deposit, the joint capsule gradually becomes thickened and fibrotic,



Fig. 183.—Slight fusiform swelling of soft tissues and thickening of periarticular tissues about midphalangeal joints. Haziness of joint spaces, slight roughening of zone of provisional calcification and atrophy of the spongy bone proximal to the joint region. Early stage atrophic arthritis (see Fig. 182). Most characteristic joint indicated by arrow. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

the osteoblastic elements within the zone of provisional calcification become active, and in places new bone formation is present. Between these areas of new bone formation there is often destruction. The appearance on the roentgenogram, therefore, in the early stage shows considerable roughening about the margins and along the bony joint surfaces. Small spicule formations are present at the joint margins where the cartilage, capsule and synovial membranes join. Sometimes there is recognized homogeneous haziness throughout the joint

space due to the filling in of the new growth of soft tissue. The bone ends become atrophic, and sometimes this atrophy is characteristically called "ground glass" in appearance. The

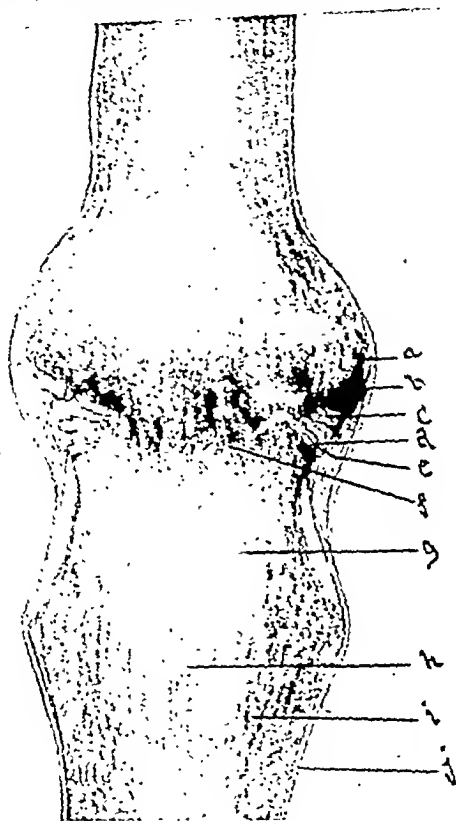


Fig. 184.—Atrophic arthritic—advanced stage. Diagram of advanced stage: *a, b, c, d, e*, very little of original structures can be identified, adhesive bands present, small cartilage and spicules of calcium deposits about joint borders; *f*, firm union with irregular remnants of zone of provisional calcification, irregular areas of atrophy; *g, h, i*, some slight secondary atrophy. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

periarticular and surrounding soft tissues often show moderate fusiform swelling.

As the condition advances, the capsule and synovial membranes are greatly thickened and thrown into folds in which cartilage sometimes deposits and later becomes ossified. This is recognizable on the radiographic films as the so-called

"joint mice." The fibrous tissue fuses across the joint space and forms a soft tissue type of ankylosis. The joint space narrows and eventually becomes obliterated owing to the destruction of the cartilage. The bone ends then come into contact and, in places, tend to fuse together. There is recognizable on the radiographic films, therefore, narrowing of the joint space or complete obliteration, early fusion of the bone ends, extensive atrophy involving the entire ends of the bone and advancing into the soft tissues, and showing the typical

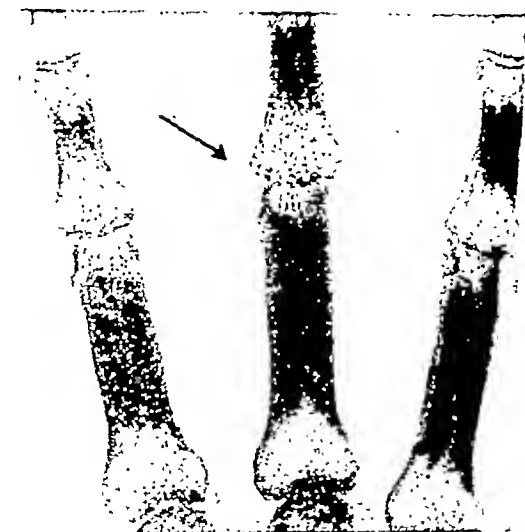


Fig. 185.—Further increase of the atrophy, narrowing of joint spaces, marked thickening of periarticular tissues, marked irregularity of the zones of provisional calcification. No atrophy of the midportions of the shafts. Intermediate stage atrophic arthritis. Most characteristic joint indicated by arrow. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

ground-glass appearance in many cases. There is now gross irregularity of the zone of provisional calcification with irregular areas of destruction, sometimes free fragments of osseous material within the joint space and, gradually, complete bony fusion across the joint. It is noted that the small spicule formation previously described never increases to the size of spur formation. The soft tissues in this stage become atrophic, although in many cases the periarticular structures remain thickened. Owing to the irregular fusion of the bones,

the axes are often thrown out of alignment, causing deviations; this is shown typically in the phalangeal and metacarpophalangeal joints, where the fingers are deviated to the ulnar side.

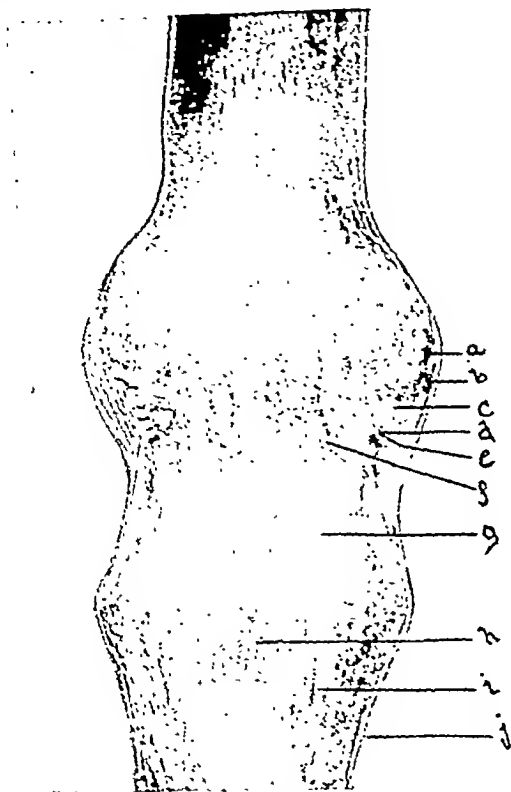


Fig. 186.—Atrophic arthritis—advanced stage. Diagram of advanced stage: *a, b, c, d, e*, same as in Fig. 184; *f*, solid bony fusion, continuation of spongy bone, fragmentary remains of zone of provisional calcification, a few small discrete areas of atrophy locally; *g, h, i*, widespread secondary atrophy throughout. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

In the *advanced stage*, there is progressive atrophy of the bone and complete obliteration of the joint space. All previously existing structural components of the joint have now disappeared and advanced atrophy is present throughout. The bone trabeculae form a continuous pattern across the previously existing joint area. This is shown on the x-ray

film by advanced atrophy throughout all bony structures, and complete disappearance of any joint architecture, although occasionally remnants of the zone of provisional calcification are preserved. The bones show fusiform dilatation occasionally, due to softening and telescoping as a result of the pressure of the bone ends just prior to fusion. In some cases it is possible to recognize continuity of both cortex and medullary space directly through the previous joint region. The

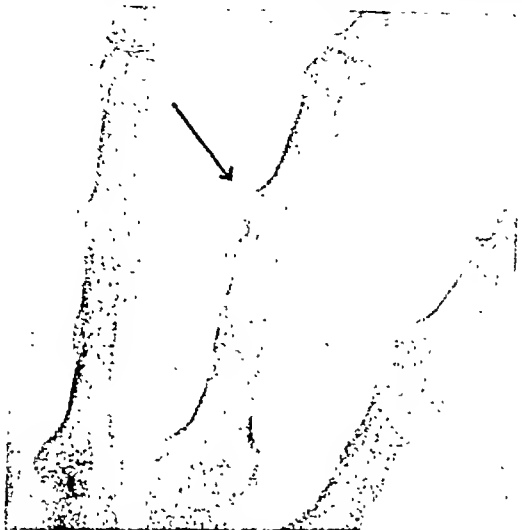


Fig. 187.—Solid bony union of the middle phalanges with continuous spongy bone. A few preserved remnants of the zone of provisional calcification. "Telescoping" of the heads of metacarpals into bases of proximal phalanges. Marked local atrophy about the joint structures and rather generalized disuse atrophy of shafts. Advanced stage atrophic arthritis (see Fig. 186). Most characteristic joint indicated by arrow. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

soft tissues at this stage have become extremely atrophic, including the muscles in the region about the affected joint.

SUMMARY OF ROENTGEN DIAGNOSTIC FEATURES IN ATROPHIC ARTHRITIS.—A summary of the x-ray diagnostic points in atrophic arthritis, in their order of sequence, would show: (1) irregularity of the bony joint surfaces, (2) all spicule formations about the joint borders, (3) homogeneous haziness throughout the joint space, (4) atrophy of the bone ends, (5) fusiform swelling of the soft tissues at a somewhat more advanced stage, (6) a ground-glass type of atrophy of

bone ends and advancing up the shafts, (7) gross irregularities and punched-out areas of the bony joint surfaces, (8) contact of adjacent bones at various points and in places

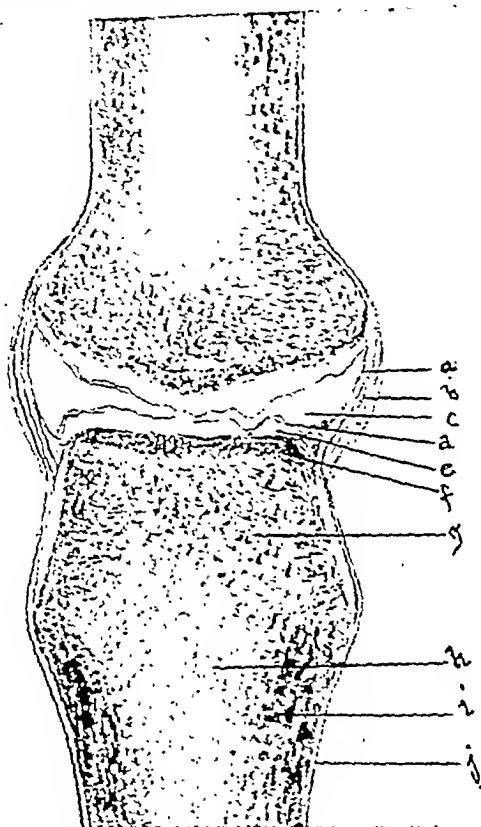


Fig. 188.—Hypertrophic arthritis—early stage. Diagrammatic illustration of pathologic changes in early hypertrophic arthritis: *a, b, c*, little or no thickening of the synovial membrane and joint capsule, joint space of normal width; *d*, perichondrium destroyed in places and proliferating elsewhere to form new cartilage; *e*, cartilage eroded and dissolved, resulting in gross irregularity of surfaces; *f*, spur formation rising from the zone of provisional calcification and extending into the junction of cartilage, bone and capsule; *g, h, i, j*, unchanged. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

fusion of the bone ends, (9) joint mice and deviations in alignment due to irregular fusion of the bone ends, and (10) thickening of periarticular tissues, but atrophy of soft tissues

generally. In the *very advanced stages* there are: (1) generalized atrophy throughout all bone structures, (2) complete disappearance of the joint architecture, (3) deformity of bone ends, with softening and telescoping of the bone structures across the previous joint space, and (4) extensive atrophy of both periarticular and soft tissues, including the muscles about the region.

Hypertrophic Arthritis.—Hypertrophic arthritis in the *early stage* shows fibrillation of the cartilaginous matrix sec-

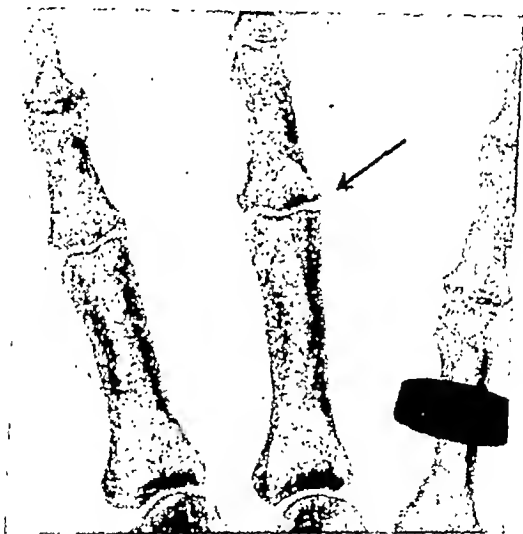


Fig. 189.—Slight swelling of soft tissues and thickening of periarticular tissues, small sharp spur formations at joint margins. Very early atrophy of the "honeycomb" type. There is very little narrowing of the joint space but a tendency to flattening of joint surfaces. Early stage hypertrophic arthritis (see Fig. 188). Most characteristic joint indicated by arrow. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

ondary to some toxic cause and resulting in erosion of the cartilage. In places the perichondrium increases in activity and attempts to lay down new cartilage islands. A similar process is present in the bone just proximal to the joint space, or the so-called zone of provisional calcification, there being in places destruction and in other places proliferation, causing a saw-tooth pattern in which the proliferated area of one side has a tendency to fit into the eroded area of the opposite side of the joint. On the radiographic film these changes are

recognized as small osteophytic outgrowths about the joint margins, generalized narrowing of the joint space, tendency to slight tilting of one bone on the other due to these irregularities, and a saw-tooth appearance of the two bony joint

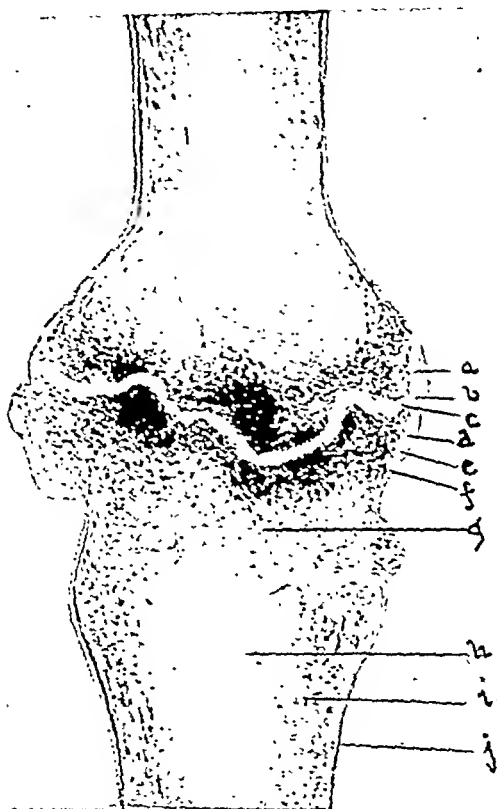


Fig. 190.—Hypertrophic arthritis—advanced stage. Diagram of advanced stage: a, b, c, d, e, capsule is thinner than normal, other structures have disappeared, two bony ends articulate and joint space irregular; f, thickening of zone of provisional calcification with formation of nodule of new bone growth; g, h, i, atrophy of the secondary or "honeycomb" type; j, periosteum unchanged. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

borders, one fitting into the other. Sometimes there is recognized a slight degree of secondary atrophy in the bone ends. This, however, is the type of atrophy which is commonly seen after application of a splint and in which the pattern of the

trabeculae is usually preserved, differentiating it from the so-called toxic or ground-glass atrophy seen in the atrophic type.

At a somewhat *later stage*, there is increase in the circumference of the bone just proximal to the joint space, due to osseous overgrowth and the formation of spurs and Heberden's nodes. There is progressive erosion of the bones and nearly complete destruction of all cartilage elements. Small

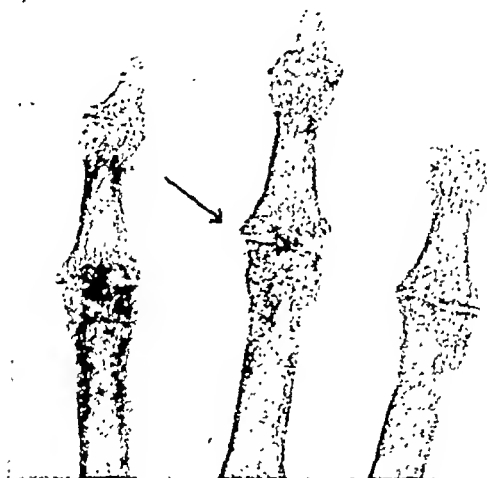


Fig. 191.—Note the apparent bony ankylosis and obliteration in terminal phalanges. This is due to the distortion of joint space, which was still preserved, and large bony outgrowths in the vicinity of the joint (Heberden's nodes). There is "mushrooming" of the terminal portions of the phalanges with widening of the circumferences of the joint surfaces. Irregular punched-out areas. Increase of density of bone just proximal to the joint spaces, most marked in the bases of the middle phalanges and rather advanced secondary atrophy throughout. Most characteristic joint indicated by arrow. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

cystlike cavitations are formed adjacent to the bony joint margins and the atrophy of the bone ends increases, but still retains its secondary or honeycombed characteristics. The periarticular and soft tissues tend to atrophy. On the radiographic films we find spur formations about the bony joint margins; these are often very well developed, irregular, and form nodes or pincer-like projections which sometimes touch but do not fuse. There is obliteration of the joint space, gross

irregularity of the bony joint surfaces, causing subluxations of the bone and a saw-tooth appearance wherein the projections from one side of the joint fit into the eroded areas of the opposite side. The circumference is broadened as a result of

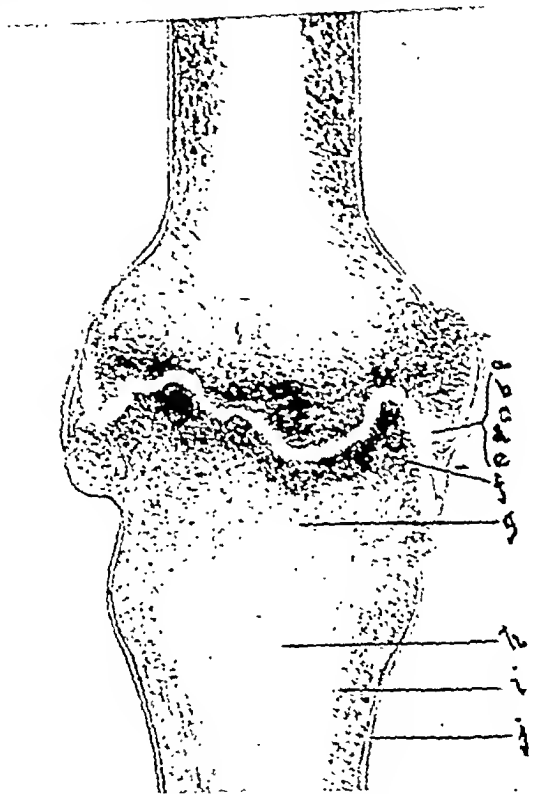


Fig. 192.—Hypertrophic arthritis—advanced stage. Diagram of advanced stage: *a, b, c, d, e*, capsule stretched between bone ends, cartilage eroded away from bone ends; *f*, zone of provisional calcification becomes the area of eburnation; spur formation and broadening of the circumference due to bony nodules but no fusion; *g, h, i, j*, secondary atrophy. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

new bone formation and there is increasing atrophy of the secondary type.

In the *very advanced stage*, the cartilage is completely destroyed and denuded bone ends come into contact. The normal joint motion is limited, and often the bone ends lock together. They never, however, fuse and the impression of

bony ankylosis is merely due to the restriction of motion caused by the saw-tooth irregularity and impingement by the spur formation. The joint space may appear, on the radiographic film, to be obliterated, but it is never actually so, this appearance being due to the outgrowth of bone from the joint margins superimposing. Extensive luxations are rather common at this stage; the shaft shows a high degree of atrophy and all surrounding soft tissues become extremely



Fig. 193.—Extensive subluxations. Note how the overgrowths fit into the notches of the opposite joint surface, especially middle phalanx. There is marked broadening of bases of the phalanges, spurs and bony overgrowths, eburnation proximal to joint margins. A few small punched-out areas, rather generalized honeycomb atrophy. Advanced stage hypertrophic arthritis (see Fig. 192). Most characteristic joint indicated by arrow. (From author's article in *Am. J. Roentgenol. & Radium Therapy*, Feb., 1936.)

atrophic. On radiographic examination the large irregular spur formations and nodes are easily recognizable. The gross irregularity of the joint space is plainly seen, except in those cases where it is obliterated by superimposed bone. The deviations in alignment and subluxations are demonstrated and the eburnation of the bone ends caused by constant friction of two bony surfaces without cartilage covering is demonstrated on the x-ray film by increase in density of the

immediate zone proximal to the joint space. The punched-out areas are often recognized at this stage and the atrophy may involve a very large portion of the shaft.

SUMMARY OF ROENTGEN DIAGNOSTIC FEATURES IN HYPERTROPHIC ARTHRITIS.—A summary of the prominent diagnostic features from the x-ray standpoint in hypertrophic arthritis, in the order of their sequence, would show: (1) small osteophytic outgrowths about the joint margins, (2) narrowing of the joint space, (3) slight changes in alignment of the bone, (4) irregularities of the bony joint surfaces, and (5) a honeycombed or secondary type of atrophy of the bone ends. At a somewhat *later stage* we find: (1) large, irregular, well-formed spurs, (2) complete obliteration of the bony joint space, (3) subluxation of the bones, (4) a saw-tooth appearance of the remaining joint space, (5) punched-out areas in the borders of the bone, (6) broadening of the circumference due to new bone formation, and (7) advanced secondary atrophy involving the shafts as well as the bone ends. In the *very advanced stage* we recognize: (1) gross irregular spur formations, (2) displacements and deviations in alignment, (3) increased density of the immediate bone ends due to eburnation, (4) complete obliteration of joint space but never fusion, (5) gross irregularity of the bone ends, due to proliferation and destruction, and (6) advanced secondary atrophy of the bone elements and also the surrounding soft tissues.

SUMMARY

By correlating the known pathologic features of the two types of chronic polyarthritis, the clinician is enabled to follow the analysis of the radiologist to better advantage and to receive considerable assistance, both as to the present stage of the joint in question and as a guide in determining active usefulness after the recession of the acute symptoms.



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THE PHYSIOLOGY OF JOINT TISSUE

ALTHOUGH joints receive most of the blows and jolts of the body, and much has been written about the alterations produced by disease, their physiology attracted little attention until recent years. In the following we shall limit our considerations to strictly *normal* functions.

The two articular structures which are chiefly involved in chronic arthritis are the *synovialis* and *cartilage*. Let us first consider the *synovialis*.

Synovialis.—The synovial membrane consists of an *external* and an *internal layer*; the latter resembles pleura or peritoneum in appearance. In the external layer numerous fringes or *villi* can be seen, largely confined to the articular margins. In them, nests of cells of the connective tissue type are clustered. By appropriate staining, globules of *mucin* can be seen within the cells.¹¹ A well defined *Golgi apparatus* in the cytoplasm of the villous cells has been described by King;¹⁷ whether this finding is confirmed remains to be seen. Various other workers^{39, 13 15} have presented evidence for the *secretory nature* of these cells. Another school² argues that, since synovial fluid resembles tissue fluids in most other respects, the synovia cannot yet be proved to possess a secretory mechanism.

Unlike cartilage, *synovialis* possesses considerable reparative ability and undergoes marked proliferation under the influence of injury, chemicals and toxins. Circulatory changes, obliteration of the lymphatics, and increased production of synovial fluid high in mucin characterize most effusions within the synovial sac.

Permeability of Synovial Tissue.—The interchange of solutes, colloids and particulate matter between the synovial

membrane and the circulatory and lymphatic systems affords some insight into the functions of synovial tissue. Kuhns¹⁹ published an extensive review of this subject and gave detailed protocols of experiments on the fate of India ink, mild silver protein, hydrogen peroxide and tubercle bacilli when injected intra-articularly. With silver protein, fluorescence could be demonstrated under the microscope by transmitted light, and when present in them the lymphatic channels were sharply outlined. Similarly, liberation of oxygen from hydrogen peroxide by lymphatic enzymes filled the lymphatic channels with bubbles of gas. India ink and tubercle bacilli were found in the regional lymph nodes after appropriate intervals. Most observers have concluded that solutes and diffusible dyes are absorbed by the capillaries of the synovial membrane, although some^{35, 36} describe staining of the regional nodes after intra-articular injection of dyes. Bennett and Shaffer³ determined the presence of egg albumin, horse serum albumin and euglobulin after intravenous injection. The first appeared in the joint cavity within five minutes, the latter two after twenty minutes. This difference in speed of permeability is probably related to the size of the molecule. In these experiments, the spinal fluid rarely contained any of the injected material whereas the glomerular membrane easily excreted egg albumin.

One may conclude that the synovialis is more permeable than either the choroid plexus or glomerular membrane and that the presence of proteins in the synovial fluid represents an elective permeability to these substances.² These large protein molecules as well as particulate matter are absorbed by the lymphatics. Passive exercise and massage greatly increase the lymph flow from a joint. In arthritis, where the joint fluids contain excess proteins and the synovialis is edematous and inflamed, the value of these procedures is self-evident.

The synovialis does not offer any barrier to diffusible substances. In fact, synovial fluid appears to be in close equilibrium with the blood stream. Thus, Pemberton and his collaborators⁶ demonstrated the rapid rise of glucose in synovial fluid after the standard glucose tolerance test. The initial values for both blood and fluid glucose were similar and the subsequent rises almost identical. In another instance, sodium bicarbonate by mouth increased the carbon dioxide combining power of both blood and synovial fluid. Others² have shown that thiocyanate and mecholyl diffuse into

TABLE I
COMPARISON OF COLLOIDS, NONELECTROLYTES AND ELECTROLYTES IN BOVINE AND HUMAN SYNOVIAL FLUID

Author.	Source.	Total solids.	Total protein.	Albumin.	Globulin.	A-G ratio.	Min. ch.	Sugar.	NPN.	Urea.	Uric acid.	Lactic acid.	Cholesterol.	HCO ₃	P.	Sol. salt.	Total base.	Na.	K.	Ca.	Mg.	pH.	Viscosity at 20°.	Specific gravity.	H ₂ O. %
Darr, Roper and Wallace.	Cattle serum. Cattle synovial fluid.	gm. 8.72	gm. 7.40	gm. 2.91	gm. 3.42	1.10	gm. .	gm. 91	mg. 21	mg. 8.5	mg. 1.84	mg. 5.47	mg. 109.8	mg. 28.8	mm. 2.2	mg. 5.56	mg. 165.7	mg. 154.1	mg. 5.37	mg. 6.6	mg. 1.76	7.42			
		2.03	0.884	0.712	0.160	2.90	0.138	66	21	8.2	1.53	3.21	110.2	28.5	2.2	4.99	143.2	115.0	4.04	3.8	1.44	7.31	3.7 to 64.0		
Cajal, Cooper and Fieber.	Human synovial fluid.	6.68	5.17	91	32	..	3.9	4.5	92.6	26.3	2.0	..	7.39	7.5		94
		4.41	1.8	1.95	1.008 to 1.040	92.7 to 93.8
Fieber.	Human synovial fluid (normal, edema, etc.).	1.20 to 6.00	1.39 to 6.92	0.45 to 3.90	0.25 to 2.65	..	0.38 to 1.95	72 to 119	19 to 29
		8.5 to 9.3	6.5 to 7.5	3.7 to 5.3	1.9 to 3.3	77 to 114	18 to 30	12 to 29	2 to 6	4.7 to 6	98.0 to 110.0	37.2 to 51.2	116.0 to 160.0	133.0 to 160.0	4.0 to 6.0	7.40	1.7 to 2.0		
Cajal, Cooper and Fieber.	Human plasma.	8.5 to 9.3	6.5 to 7.5	3.7 to 5.3	1.9 to 3.3	77 to 114	18 to 30	12 to 29	2 to 6	4.7 to 6	98.0 to 110.0	37.2 to 51.2	116.0 to 160.0	133.0 to 160.0	4.0 to 6.0	7.40	1.7 to 2.0		
		8.5 to 9.3	6.5 to 7.5	3.7 to 5.3	1.9 to 3.3	77 to 114	18 to 30	12 to 29	2 to 6	4.7 to 6	98.0 to 110.0	37.2 to 51.2	116.0 to 160.0	133.0 to 160.0	4.0 to 6.0	7.40	1.7 to 2.0		

the joint readily. The similarity between the chemical make-up of blood and synovial fluid can be seen from inspection of Table 1.

Chemical Constitution.—The reported values for total solids and proteins in human synovial fluid are probably high, since most of the determinations were done on patients with joint effusions. The analyses of fluid from joints at autopsy may likewise be abnormal, but perhaps more nearly approach the values found in health. Albumin accounts for the bulk of the protein exclusive of mucin. The synovial membrane, as already indicated, is partially permeable to certain colloids of the blood. The levels of nonelectrolytes and electrolytes of synovial fluid are in close aggrement with the serum concentrations and meet the requirements of the Donnan equilibrium ratio with the exception of calcium. This balance indicates that the synovial membrane is permeable to these diffusates. Bauer and his collaborators² are inclined to believe that synovial fluid is a plasma dialysate to which "mucin is added as the fluid passes the connective tissue surrounding the joint."

The high viscosity is largely due to *mucin* which contributes its great lubricating value. Jones¹⁴ has demonstrated that synovial fluid is spread over the joint surfaces as a film. Friction resulted if the speed of motion was not sufficient to maintain a pressure film. Similarly, the coefficient of friction was fourteen times as great in joints kept dry as in those well lubricated. Heat, grating, and wear of the articular ends were detectable in the dry joints after prolonged artificial motion.

Cytology of Synovial Fluid.—Table 2 lists the total leukocyte counts and the differential ratios for human, rabbit and cattle synovial fluids. These represent normal values which, however, may show differences between joints in the same species. In the synovial fluid found in arthritic joints, the total leukocyte count rises and the proportion of polymorphonuclears increases. Hypertrophic arthritis and scurvy are the two exceptions; in these conditions, the total counts may be low or show slight increases. Figures for rheumatoid and hypertrophic arthritis are included.

Cartilage.—Hyaline cartilage, which clothes the articular ends of bone, is relatively poor in cells and rich in matrix. Roughly, the cells of the central portion lie in three strata: an upper flattened layer, an irregular intermediate zone, and a deeper group arranged vertically.¹¹ It is thought that growth occurs from centrally placed foci both toward the

TABLE 2
CYTOLOGY OF SYNOVIAL FLUID

Author.	Source.	Total cell count.	Differential count—per cent.						
			Mono-cytes.	Chs-mato-cytes.	Mac-ro-phages.	Lym-pho-cytes.	Poly-mor-pho-nu-clears.	Syn-ovial lining cells.	Un-classi-fied.
Key ¹⁰	Rabbit's knee.	175-225	42-84	4-28	3-29	..	0-12	0-7	0-10
Warren, Bennett and Bauer ⁶ ...	Cattle—astrag- lotalibial joints.	112-182	36.4	15.0	3.9	40.1	2.2	1.2	1.2
Warren, Bennett and Bauer ⁶ ...	Cattle—carpo- metacarpal joints.	213-222	63.0	7.2	3.0	23.0	1.2	1.7	1.0
Bauer <i>et al.</i> ⁸ ...	Human—knee, autopsy.	13-180	47.9	10.1	4.9	24.6	6.5	4.3	2.2
Kling ¹⁸	Human—knee, normal.	0-50	0-20	..	*	5-35	0-15	35-60	...
McEwen ¹⁴	Human—nor- mal.	125-200	5-10	0-13	5-8	8-16	7-27	3-7	12-16
Kling ¹⁸	Human—ar- thritic.	37,277	12.0	20.0	64.0	4.0	...
Kling ¹⁸	Human—de- generative ar- thritis.	870	20.0	*	..	44.0	15.0	21.0	...

* Recorded with monocytes.

joint surface and toward the subchondral bone. With aging, the proportion of matrix to cells increases. Thus, in young calves an average of 133,000 cells per cubic millimeter was found; in adult steers this decreases to 47,000 and in old animals to 33,000.³⁴

The lateral margins of articular cartilage have been described as covered with a delicate extension of synovial membrane;¹¹ in this respect it resembles the hyaline cartilage of the ribs which is partially covered by perichondrium. In certain birds, *e. g.*, the ostrich, the perichondrial layer persists throughout life. The lateral portion receives its blood supply from the *circulus articuli vasculosis*, which was first described by John Hunter. Figure 194 illustrates this. The central portion, on the other hand, is considered avascular by most observers. The deeper cellular layer is penetrated by vessels from subchondral bone.^{11, 4} In young animals, injection studies indicate that small vessels sometimes traverse the central portion.⁴

Nutrition of Articular Cartilage.—The nutriment of articular cartilage is of more than academic interest since it must come directly through vascular channels or exuded plasma filtrate therefrom, or by imbibition from the synovial

fluid. Toynbee first proposed that the subchondral vessels supply articular cartilage with nourishment; subsequently, Strangeways and others suggested that synovial fluid furnishes its chief pabulum.³² Presumably alterations in the intra-articular pressure (normally -2 to -12 cm. of water) induced by motion, together with differences in the diffusion gradients of solutes between synovial fluid and cartilage, aid in the imbibition. One of the most cogent reasons for the

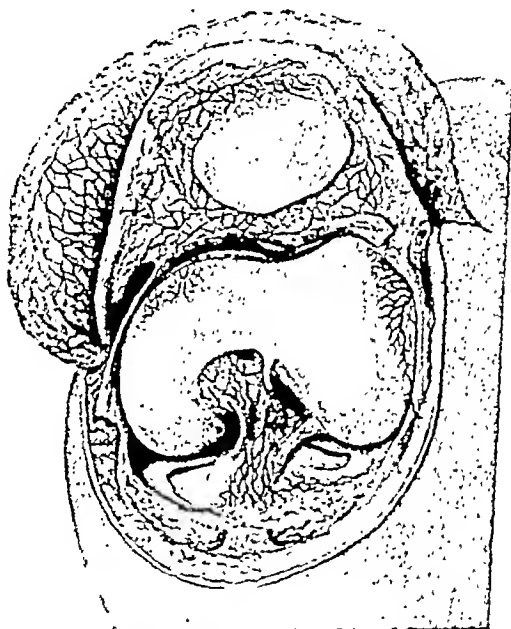


Fig. 194.—Blood vessels of the synovial membrane and the circulus articulari vasculosis in the knee joint of a human fetus at term. The arborization of small vessels at the cartilaginous margins can be readily seen. (From Fisher, "Chronic Nontuberculous Arthritis," reproduced by permission of The Macmillan Company, publishers.)

latter theory is the behavior of *loose bodies*, either traumatic or artificial, in the joint. A loose body composed of bone soon undergoes necrosis, while one of cartilage remains viable for months.

The depth to which oxygen (and possibly glucose) penetrates by diffusion at its concentration in the synovial fluid (the diffusion constant) is less than the thickness of cartilage.^{5, 34} The avascularity of the central portion predisposes

it to the degenerative changes in arthritis.¹¹ Figure 195 illustrates an ulcer on the medial condyle of the right metacarpal of a five-year-old steer. The marginal lipping has been explained by Bauer¹ on the basis of repeated strain which the synovial membrane exerts during motion on the perichondrium at the articular margins. This proliferation, with its eventual formation of new bone in the lateral margins, is due to the greater reparative ability of marginal cartilage, probably conditioned by the more adequate blood supply.

Protective Action of Synovial Fluid.—In disease, synovial fluid attempts to protect cartilage in several ways. Keefer



Fig. 195.—A deep ulceration (indicated by the arrow) in the central portion of the articular cartilage. This extends down to subchondral bone. Proximal end, medial side of the right metacarpal of a five-year-old steer. X is an artefact.

*et al.*¹⁵ have shown that the fluid possesses an antitryptic quality which inhibits the trypsin elaborated by the leukocytes in purulent effusions. Likewise, the acid-binding ability of mucin exerts a protective action against acid metabolites formed in certain types of joint disease. It is known that acid destroys cartilage,¹⁸ and it has been repeatedly shown that the pH of purulent effusions is lower than the normal.

Chemical Constitution of Cartilage.—The matrix of cartilage yields on decomposition chondroitin-sulfuric acid, albuminoid, glycogen and inorganic salts.²⁵ The cells consist of coagulable protein which has not been analyzed. The water content of articular cartilage ranges from 67.6 to 77.2 per

cent, depending on the age of the material.^{24, 25, 37} Bone has an average water content of about 44 per cent. The glycogen content is much higher in young animals than in old. The chondroitin-sulfuric acid portion together with mucin will be considered as a whole. These substances were called "mucoproteins" by Levene.²¹ They more properly should be termed "mucopolysaccharides,"²⁸ since they may occur either as free polysaccharides or as protein salts; they have in common an amino hexose (glucose, galactose or mannose) conjugated with uronic (glucuronic) acid. The complex in synovial mucin is hyaluronic acid which consists of equimolar parts of glucosamine, acetyl and glucuronic acid. Similar compounds have been described in the aqueous and vitreous humors, the uveal tract of the eye, the umbilical cord, in the group A streptococcus, and Type I pneumococcus. No sulfate occurs in this group. The sulfate-containing complexes include chondroitin-sulfuric acid of cartilage and similar compounds found in tendon, gastric mucin, the cornea, aorta, sclera and heparin. Chondroitin-sulfuric acid consists of equimolar parts of acetic acid, chondrosamine (2-aminogalactose), glucuronic acid and sulfuric acid.

Meyer²⁸ succeeded in demonstrating an interesting physical property of artificial chondroitin-sulfuric acid-protein complexes; gelatin, globin and egg albumin were the artificial proteins added. The gelatin complex coalesced in the cold to form elastic mats or sheets; the edestin compound produced elastic fibers, similar to the elastic fibers of connective tissue. From chemical analysis it seemed probable that hyaline cartilage is a salt of chondroitin-sulfuric acid with a protein-like gelatin.

Various workers have described *enzymes*^{31, 27, 28, 33, 7, 29} which hydrolyze several of the mucopolysaccharides: chondroitin-sulfuric acid, those of the umbilical cord, hemolytic streptococcus, pneumococcus and mucin. These enzymes have been isolated from various bacteria and from extracts of spleen and testis (these are both of mesodermal origin). Some biologic significance may be attached to the similarity of the mucopolysaccharides of group A streptococcus, the uveal tract and the synovial mucin, since an upper respiratory infection with the streptococcus may initiate joint symptoms and subsequently involve the eye; the frequency with which this happens in the patient with rheumatic fever or rheumatoid arthritis needs no comment. Possibly a common antigenic quality exists in these related mucopolysaccharides.

Changes in Cartilage Due to Calcification.—Calcification in cartilage has been studied with the tissue culture technic.¹⁰ In the embryonic chick, calcification of osteoid could be accelerated by immersion in a medium of calcium with both organic and inorganic phosphate. Cartilage hypertrophies early, but does not begin to calcify before the fifteenth day. The hypertrophied cartilage produces phosphatase to a marked degree. The total base of cartilage becomes concentrated before calcification proceeds.²² When cartilage is con-

TABLE 3
METABOLISM OF JOINT TISSUES

Author.	Type and source of material.	Respiration.		Glycolysis.		Respiratory quotient.
		Spontaneous.	With dye.	Aerobic.	Anaerobic.	
Dickens and Weil-Malherbe. ⁹	Costal cartilage.	0.45	...	1.22	1.60	} 0.86†
Bywaters. ³	Equine articular cartilage.	0.005	0.065	0.100	0.091	
Rosenthal, Bowie and Wagoner. ²¹	Bovine articular cartilage } Young	0.088	0.144*	0.910	1.12	
	} Adult	0.024	0.142*	0.420	0.438	
	} Old	0.008	0.130*	0.248	0.259	
Bywaters. ³	Equine synovial membrane.	0.80	increased	1.7	0.3	0.71
Bywaters. ³	Fibroblasts.	22.0	...	8.0	45.0	

All figures except those for the respiratory quotient indicate the amount of gas absorbed (respiration) or produced (glycolysis). The negative and positive signs are omitted to avoid confusion.

* In the presence of dye and glucose, these values increase to 0.247, 0.185 and 0.150 for young, adult and old cartilage, respectively.

† Measured after addition of dye.

verted to organic matrix of bone, the organic sulfates decrease and nitrogenous constituents increase. The drop in total sulfate may possibly be due to a loss of chondroitin-sulfuric acid, and this may initiate a precipitation of inorganic salts because of the lowered pH. Both inorganic and organic phosphates are concentrated in calcifying cartilage.

Metabolism of Articular Structures.—Until quite recently, relatively few investigations had been carried out on the metabolism of joint structures. Table 3 lists the significant data. Figures for fibroblasts are shown for comparison.

The *respiration* of cartilage is sluggish. The low values for equine articular cartilage agree with those for aged bovine material; the decrease in the latter from infancy to old age is probably due to the drop in the number of cells. Respiration of synovial membrane is much higher, but does not approach that of fibroblasts. *Glycolysis* in both cartilage and synovial membrane is on a much higher level than is respiration, and per cell is approximately that of other adult tissues. The respiratory quotient for synovial membrane suggests that only fat is oxidized; that for cartilage, measured after addition of methylene blue, indicates that both fat and protein are utilized. The glycolysis of inflamed synovial membrane and of a human enchondroma markedly exceeded normal values.⁵

Enzymes.—Dehydrogenases (enzymes which remove hydrogen from tissue metabolites) are present in both cartilage and synovial membrane.^{5, 34} Respiratory power of cartilage decreases with aging; the gradual failure of oxidative ability in cartilage probably makes it susceptible to degenerative changes. These enzymatic groups are thermolabile. Calf cartilage possesses an active enzyme system which dephosphorylates and/or deaminizes adenine derivatives; hypoxanthine is the end product of these reactions.²⁸ In muscle, the oxidation of adenine compounds stops at inosinic acid, an intermediate metabolite higher in the oxidative scale than hypoxanthine. Various phosphorylated and nonphosphorylated carbohydrates are attacked by other enzymes, yielding lactic acid as a final step.

Effect of Hormones.—Acid extracts of the pituitary, as well as glandular implants, induce fibrillosis and vacuolization of the cartilage matrix in immature female guinea-pigs. Both retrogressive and regenerative changes were seen in the resting cells, which finally calcified.³⁸ In the chondro-osseous junctions of ribs, hyperplasia of the perichondrial and periosteal cells, with an accelerated conversion into cartilage cells, was observed after prolonged use of the extracts. Thyrotropic and gonadotropic activity was excluded; thyroidectomy and oophorectomy did not alter the effects noted. Oophorectomy resulted in hypertrophy and hyperplasia of the vesicular columnar cells, reduction in the amount of intercellular tissue, and a delay in calcification. Presumably, ovarian hormones retarded the maturation of cartilage and restricted its growth. These findings, though unconfirmed as yet, may help to explain the frequently development of arthritis at the menopause. Relaxation and stretching of the ligaments of the

symphysis pubis have also been noted after use of pituitary extracts.

Effect of Other Substances.—The integrity of most intercellular material depends, in part, on an adequate amount of *cevitamic acid*. The matrix of cartilage in scorbutic animals exhibits changes similar to those seen in dentin and bone. Wolbach⁴¹ believes that cevitamic acid plays an essential role in the deposition and maintenance of collagen, which "binds" intercellular ground substance together. Cartilage is particularly rich in *collagen*, as we have noted above. The collagen fibers may be easily demonstrated by soaking the articular end of a bone in brine.¹¹

SUMMARY

Joints are tissue spaces or clefts derived from the mesoderm. They consist of a number of related structures, chief of which are synovial membrane, synovial fluid and cartilage. The former is highly cellular, has a rich vascular supply, and repairs readily. The latter is probably avascular in the central portions and is poor in cells. Synovial fluid serves to lubricate and possibly nourish articular cartilage. Most of the serum electrolytes and nonelectrolytes pass the synovial barrier freely. Mucin is the component to which synovial fluid owes its essential characteristics. Both mucin and cartilaginous matrix are mucopolysaccharides, closely related chemically. The peculiarities of cartilage metabolism afford a possible explanation of its tendency to exhibit degenerations and of the inability to repair itself. Synovial membrane, on the other hand, has a metabolism per cell equivalent to that of other adult tissues. The influence of hormones on articular structures is only partially understood. Many other phenomena of joint physiology and structure remain as unsolved problems for the future.

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CLINIC OF DRS. G. E. FARRAR, JR., AND F. W. RAYBURN

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THE BLOOD IN ARTHRITIS

ARTHRITIS is associated with alterations in the cytology and chemistry of the blood. Some of these changes are of value in the clinical management of arthritic patients. In the differential diagnosis of the five frequent types of chronic joint disease—atrophic arthritis, rheumatic fever, gonorrheal arthritis, hypertrophic arthritis and gout—six blood tests aid in¹ the clinical diagnosis and, in atypical cases, indicate the nature of the disease process. These blood tests are the *erythrocyte sedimentation rate*, *Schilling hemogram*, *complement fixation test for gonococci*, *blood uric acid test* and the *tests for streptococcus agglutinins* and *antistreptolysins*. The sedimentation rate is the most sensitive criterion of the activity of atrophic arthritis and rheumatic fever. An understanding of the degree of activity of the disease is necessary for the physician to determine the optimum time for surgical intervention or for other forms of active therapy. The sedimentation rate also indicates the patient's response to treatment. Finally, these blood changes, including the recognition of anemia, provide specific indications for the supportive therapy of these chronic diseases. Only those marked and characteristic alterations which are applicable in the routine clinical laboratory will be considered.

Atrophic Arthritis.—The cytologic changes are mild anemia² of normocytic or microcytic type, a normal total leukocyte count and a normal differential leukocyte count except for an increase in the younger forms of the polymorphonuclear neutrophil.

Anemia does not appear until the disease has been active for several weeks. The reticulocytes, the icterus index and the urinary excretion of urobilinogen are normal or actually

decreased. The bone marrow shows an increased number of normoblasts and pronormoblasts. The erythrocytes of the blood are normal in size and shape or slightly smaller and definitely paler than normal. Many factors contribute to the development of this anemia; dietary deficiency due to anorexia and impaired intestinal absorption, as well as inhibition of erythropoiesis, appear to be the most important causes.

The *red blood cell count* is affected by the condition of the peripheral circulation as manifested by the cold and pale or cyanotic skin over chronically involved joints. Pemberton and his associates³ found that the erythrocyte count in the first drop of blood from a stab wound in an arthritic finger is lower (about 300,000 per cu. mm.) than in the later free-flowing drops of blood. Alteration of the peripheral capillary circulation was confirmed by direct observation of the capillary loops in the fingernail beds.⁴ Hench⁵ believes these capillary abnormalities are an inconstant complication of the rheumatoid syndrome.

The *white blood cell count* is within normal limits in chronic cases. In cases with an acute, febrile onset⁶ a leukocytosis of 12,000 to 20,000 is present, with an increase of neutrophils in the differential count to 70 to 90 per cent; monocytes and lymphocytes decrease and eosinophils disappear. The *Schilling hemogram* shows a shift to the left. This increase in the immature neutrophils is more simply measured by determining the *filament/nonfilament ratio*, i. e., the proportion of neutrophilic leukocytes without segmented nuclei. With the glass slide films of the routine clinical laboratory, the maximum normal nonfilament count is 16 per cent of the total leukocytes. On thick and deeply-stained blood films an erroneously high nonfilament count is obtained because shrinkage and dark color make recognition of nuclear segments difficult. In chronic atrophic arthritis with very slight temperature elevation, the leukocyte count is within normal limits of 4,000 to 11,000, and in some cases is below normal. Although the differential count is normal, the nonfilamented neutrophils are usually increased. Among 234 cases of atrophic arthritis collected from the literature,^{7, 8, 9, 10} 147 showed a nonfilament count of more than 16 per cent; and among 392 cases^{6, 7, 8, 9, 10, 11, 12} the count was greater than 8 per cent in 346 cases. A normal nonfilament count usually excludes rheumatoid arthritis. An increased count indicates atrophic arthritis, a mixed form of arthritis including atrophic features, an osteoarthritis with a super-

imposed active infection or a suppurative arthritis. A normal nonfilament count is often present during inactive phases of atrophic arthritis.

The *erythrocyte sedimentation rate* is increased in all active cases of atrophic arthritis. Among 568 cases collected from the literature,^{6, 7, 8, 11, 12, 13, 14, 15, 16, 17} 523, or 92 per cent, showed increased sedimentation rates. Only 8 per cent of these cases had normal rates, whereas 60 per cent of 254 cases of osteoarthritis and 75 per cent of 149 cases of fibrositis had normal rates of sedimentation. An increased rate may not be present during the first weeks of acute cases of atrophic arthritis or during the early months of the more insidious type of case,⁶ but the increased rate persists for some time after the symptoms and physical signs in the joints have disappeared. In active cases the rate is markedly increased—usually about three times the normal for the method employed.¹ Unfortunately, the endless modifications of the sedimentation test in recent years have discouraged¹⁸ many clinicians from using this valuable test in the management of atrophic arthritis and other chronic diseases. In recent years in this clinic, we have returned to the use of a simple sedimentation method that is suitable for use in the office of the busy physician.

Technic and Interpretation of the Blood Sedimentation Test.—With the multiplicity of technics now in use, it is impossible to compare quantitatively the observations of different physicians. Cutler, Park and Herr²² have emphasized the clinical significance of the three phases of the sedimentation phenomenon—the phases of aggregation, sedimentation and packing. Anemia alters the sedimentation rate most in the packing phase. From the clinical point of view, the rate during the sedimentation phase is the most important. Since the character of the plasma affects the rate more than the quantity of the plasma in this sedimentation phase, correction for anemia is often a false correction. Hence, the course of sedimentation is of more clinical value than the total fall at the end of one hour.^{22, 23}

Cutler describes four types of curves. The horizontal and diagonal lines and the diagonal and vertical curves (see Fig. 196) illustrate in increasing order the severity of the disease process. The laboriousness of making readings of the level of the sedimenting erythrocytes every five minutes for one hour has led to many efforts²⁴ to develop a method that requires only a single reading at one hour, with suitable correction factors for anemia. With the large-bore tube used by Cutler, it will be seen on the chart that the packing phase is reached at about thirty minutes with the most rapidly settling blood. Hence, this method is applicable for use with a single reading at thirty minutes in the busy office or laboratory. From the clinical point of view, the second thirty minutes is of less importance. We are using 10 mg. of dry potassium oxalate for exactly 5 cc. of venous blood. The tubes must stand exactly vertical during sedimentation and the temperature of the blood must be that of room temperature (22° to 27° C.).

Although the total serum protein level is not significantly altered in atrophic arthritis, the average *serum albumin* fraction was decreased and the *globulin* fraction increased in ninety-eight cases;^{16, 25, 26} *plasma fibrinogen* was increased in fifty cases.^{16, 25} *Plasma cholesterol* concentration tends to be near the lower limit of normal.⁷ The fasting blood sugar level is usually normal, but many patients with active rheumatoid

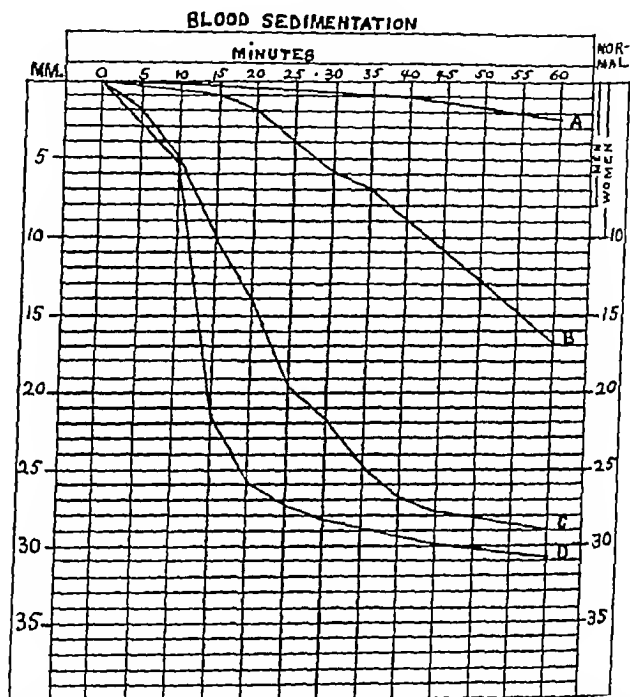


Fig. 196.—Graphic chart of the sedimentation rate. A, Horizontal line; B, diagonal line; C, diagonal curve; D, vertical curve. (From J. Cutler, *Am. J. Med. Sc.*, 171: 882, 1926.)

arthritis show a *decreased glucose tolerance*.²⁷ The blood sugar rises to abnormally high concentrations at one hour after glucose administration and returns to normal within the usual three-hour period. Most patients with atrophic arthritis are eating a low carbohydrate diet either because of anorexia or because of the frequently prescribed low carbohydrate diets. The effect of the preceding dietary on the glucose tolerance, as pointed out by Conn,²⁸ is to be considered

as an explanation. However, the glucose tolerance returns to normal as the arthritis subsides, in spite of the continuation of a low carbohydrate diet.²⁰ Hence, impaired glycogenesis seems to be associated with atrophic arthritis.

*Impaired liver function*³⁰ has been observed with the azorubin-S excretion test in 60 per cent of fifty cases, with the hippuric acid test in 62 per cent, with the bilirubin excretion test in 48 per cent, and with a serum albumin of less than 4.5 gm. per 100 cc. in 68 per cent. Serum calcium, inorganic phosphate and phosphatase are normal.⁸ Treatment with massive doses of vitamin D does not alter the calcium, phosphate or phosphatase.³¹ *Blood uric acid* concentrations near the upper limit of normal are observed in some cases. *Plasma cevitamic acid* levels are low unless the intake of vitamin C in the diet is increased to two to four times the normal requirement.³²

The presence of *agglutinins* for hemolytic streptococci in high titer¹ in the blood of patients with atrophic arthritis has been established in large numbers of cases. Since extensive investigations have not confirmed the findings of streptococci in the blood stream of atrophic patients,¹ the significance of these agglutinins is unknown. However, high titers are common in atrophic arthritis and rare in other forms of arthritis. Their presence is of diagnostic value in atypical cases. The titer does not parallel³³ the duration or the severity of the disease either clinically or as manifested by the sedimentation rate.

Hypertrophic Arthritis.—Anemia is uncommon in osteoarthritis. The total and differential *white blood cell counts* are likewise within normal limits unless some complicating infection is present. The *nonfilament count* may be slightly increased; there were more than 16 per cent of these nonsegmented neutrophils in fifty-three of 100 cases studied by Hartung and his associates,⁷ but the average count in these fifty-three cases was only 21.6 per cent. The average count in their ninety-six cases of atrophic arthritis was 29.6 per cent. Collins¹² has called attention to the correlation of increased nonfilament counts with the presence of large cystic areas in the head of the femur or in the acetabulum in cases of *malum coxae senilis*. Among seventeen cases of osteoarthritis, chiefly confined to the hip, six cases had large cystic areas and a shift to the left of the Arneth count. The remaining eleven cases with no cystic areas or only small ones by roentgen examination had a normal Arneth count. Aseptic necrosis

in these cystic areas may explain this change in the neutrophils, but it is strange that normal sedimentation rates were reported in these cases.

The *sedimentation rate* is usually normal. It was normal in 152 (60 per cent) of 254 cases collected from the literature;^{9, 10, 12, 14, 18, 24} in the remaining 102 cases it was only slightly increased in contrast to the marked increases observed in atrophic arthritis. Serum protein concentrations are very little affected. *Serum albumin* was slightly decreased in seventy-five cases;^{10, 25, 26} *serum globulin* was slightly increased in twenty-three cases^{10, 25} but unchanged in fifty-two cases.²⁰ Aldred-Brown and Munro²³ have pointed out that nonarthritic individuals of a similar age group and economic status show a slightly lower serum albumin and a slightly higher globulin than exists in healthy young adults. *Plasma fibrinogen* was slightly increased over the normal range for youth but to the same extent in both the osteoarthritic and the nonarthritic control group.

Fasting *blood sugar* levels are normal; in eleven of fifty cases studied by Haden and Warren,³⁴ a diabetic type of glucose tolerance curve was observed but this is not unusual for this age group of people. The *serum cholesterol* shows a high normal level.⁷ Serum calcium, inorganic phosphate and phosphatase are within normal limits. The metabolism of calcium and phosphorus is normal. The increased serum phosphatase activity in metastatic neoplasm to bone and Paget's disease of bone differentiates these conditions from hypertrophic arthritis.^{18, 35} Blood uric acid is usually within normal limits.

Fibrositis.—This syndrome is characterized by the normality of all blood findings.¹⁵ When there are no infections or other conditions affecting the blood in patients with fibrositis, there is no anemia, no leukocytosis, no increase in non-filamented neutrophils, no increase in the sedimentation rate and no change in the concentration of the several clinically recognized serum proteins. The sedimentation rate was normal in 112 of 149 cases;^{12, 13, 15, 16} the other thirty-seven cases showed only slight and often questionable increases in the rate. The Arneth count was normal in 104 cases of fibrositis.¹²

Rheumatic Fever.—In most respects the blood changes of rheumatic fever resemble those of rheumatoid arthritis, except that acute febrile episodes are much more common. *Anemia* of normocytic type develops, if the febrile period is prolonged over several weeks' time.³⁶ This anemia does not

respond well to iron or liver therapy, and large doses of vitamin C are likewise ineffective. When the joints are acutely inflamed, a *leukocytosis* of 15,000 to 25,000 is present with an increase in the neutrophilic leukocytes and in the nonfilamented forms. *Eosinophils* are decreased or absent. The white blood cells return to normal as the fever and the joint manifestations subside, and during convalescence eosinophils are increased. In chronic, low-grade rheumatic activity, the eosinophils persist but disappear whenever an exacerbation occurs.³⁷

The *sedimentation rate* is markedly increased and is the most sensitive criterion for the activity of the disease. Bed rest should be continued until the sedimentation rate becomes normal. The persistence of an increased rate of sedimentation for weeks in a clinically inactive case of rheumatic fever suggests the coexistence of an active focal infection which should be searched out and treated by conservative medical or surgical measures. The sedimentation rate is rarely increased in an uncomplicated common cold or in chronic tonsillitis but is elevated in acute pharyngitis and influenza.³⁸ In chorea a slight and very transient increase in sedimentation rate appears. The onset of congestive heart failure results in a decrease in a previously rapid sedimentation rate. During the "silent phase" following an upper respiratory infection, a rising sedimentation rate forebodes an oncoming rheumatic exacerbation.³⁹

Serum globulin and *fibrinogen* are increased; *albumin* decreases.

A *high antistreptolysin titer*⁴⁰ is characteristic of patients with rheumatic activity. Hemolytic streptococcal infections³³ such as erysipelas and scarlet fever have a high titer, but other arthritic disorders do not. Antistreptolysin is a substance in the blood which neutralizes the hemolytic action of the hemolytic streptococcus.

The *formol-gel test* roughly parallels the sedimentation rate.⁴¹ Schultz and Rose⁴² believe that this test follows the activity of rheumatic carditis more closely than does the sedimentation rate.

Gout.—An *increased blood uric acid concentration* during an acute arthritic attack confirms the diagnosis of gout.⁴³ In 90 per cent of Hill's ninety-one cases of gout, the blood uric acid was greater than 4 mg. per 100 cc. However, typical tophaceous gout occurs without an increased blood uric acid. Jacobson⁴⁵ found that the serum uric acid was continuously

elevated in gouty patients without significant further increases at the time of the acute attack. Blood urea nitrogen should be determined to exclude nephritis in the differential diagnosis.

The *sedimentation rate* in chronic gout is usually normal. During an acute podagra the rate is very rapid. In an arthritic patient a rapid decrease of the sedimentation rate to normal in a few days' time suggests gout⁴⁴ rather than rheumatoid arthritis. However, the sedimentation rate does not parallel the blood uric acid level.

Serum protein concentrations show no significant abnormality other than the tendency of the older age groups to have a slightly higher globulin concentration.^{25, 26}

Anemia⁴⁶ does not develop due to gout alone. The total *leukocyte count* rises during an acute attack of gout and the differential shows an increase in neutrophils. Gibson and Kersley⁴³ found the nonfilamented forms (Arneth count) to be increased as much in seventy-two cases of acute gout as in 345 cases of rheumatoid arthritis.

Suppurative Arthritis.—These acutely inflamed joints resulting from invasion by the pyogenic cocci show a marked neutrophilic leukocytosis with an increase in the nonfilamented forms, an absence of eosinophils and a marked increase in the sedimentation rate. Anemia appears if the septic process persists for any length of time. Joints affected by septic emboli in cases of *subacute bacterial endocarditis* show similar but less severe changes in the blood. Monocytes are often increased up to 15 per cent in the differential and may be actively phagocytic as indicated by the presence of erythrocytes within these cells on the blood films; these large cells are more often obtained from puncture of the lobe of the ear than from the finger.

Gonorrheal Arthritis.—The leukocyte count varies from 9,000 to 23,000, with 70 to 80 per cent neutrophils and an increase in the nonfilamented forms. Eosinophils persist and the sedimentation rate is markedly increased. The *complement fixation test* for gonococci is positive in cases of two or more weeks' duration.⁴⁷

Brucellosis.—Arthritis may be the prominent clinical feature in *undulant fever*. In addition to the skin test, agglutination and opsonocytophagic tests on the blood are usually necessary to establish the diagnosis. In serious febrile cases,⁴⁸ leukopenia with an absolute increase in lymphocytes is present. Immature lymphocytes and plasma cells are numerous and nonfilamented forms of eosinophils as well as neutrophils

are increased. In cases with arthritic manifestations the sedimentation rate is increased. A mild hyperchromic, macrocytic anemia is present.

TREATMENT AND THE BLOOD IN ARTHRITIS

Anemia.—In active atrophic arthritis, the anemia responds poorly to iron and/or liver medication. Early in the course of acutely active cases, *transfusions* often exert a dramatic influence. The appetite improves, the anemia is corrected, and the low-grade fever and the joint swellings subside. The sedimentation rate decreases by as much as one half of its previous level. In two thirds of the forty-eight cases reported by Thompson, Wyatt and Hicks,⁴⁹ clinical improvement was progressive; in the other third, an increase in the sedimentation rate again occurred and was associated with an aggravation of the symptoms. The course of the disease often appears to be shortened by transfusions of $\frac{1}{2}$ to 1 pint of blood, repeated weekly for two to six weeks.⁵⁰ In chronic cases, transfusions give temporary symptomatic improvement and are of supportive value in cases resistant to treatment, in debilitated patients and in those with a persistent severe anemia.

Anemia demands a *diet* with ample protein content—about 1 gm. per kilogram of ideal body weight. The diet should include eggs and lean meat daily. *Iron* is needed in adequate doses, such as ferrous sulfate, 3 grains by mouth three or four times a day before meals. In the rare cases with abdominal distress on this medication, it may be given after meals without difficulty. If achlorhydria is demonstrated, or if it can be clinically suspected because of a clean, red tongue, dilute *hydrochloric acid* (U.S.P.), in doses of $\frac{1}{2}$ to 1 teaspoonful in a full glass of water, should be sipped through a straw during each meal. Patients who refuse to accept this sour medication may be given *glutamic acid hydrochloride* in capsules, one before, during and after each meal. When anorexia is present and the clean tongue is swollen and inflamed, vitamin deficiency exists and may be improved by the use of *brewer's yeast* powder in doses of $\frac{1}{2}$ to 1 ounce three times daily. This powder may be made palatable by suspension in milk or fruit juice. Intramuscular *liver extract* injections may also be used for this purpose in doses of 10 units (U.S.P.) daily or at least three times weekly. A dilute liver extract is preferred.

Neutropenia.—A decrease in the total white blood cell count with a decreased number of neutrophils and an increased proportion of nonfilamented forms is frequent in chronic atrophic arthritis. Gibson⁵¹ describes another group of emaciated cases with anemia in whom the neutrophils are increased in number in a relatively normal total leukocyte count and the nonfilamented forms are decreased rather than increased. We have observed both types of blood picture in the same patient at different times.

ETIOLOGY.—The etiology of chronic neutropenia is vague because of its many and obscure causes. Overwhelming infection, which may cause neutropenia, is rarely present in atrophic arthritis. Four causes must be considered: *allergy*, *nutrition*, *endocrine dysfunction* and *drug idiosyncrasy*.

Leukopenia is frequent in simple *malnutrition* and both an inadequate dietary and impaired intestinal absorption⁵³ exist in severe rheumatoid conditions. Neutropenia is associated with *adrenal insufficiency*, as manifest in Addison's disease. Weakness, fatigue and hypotension are frequent in atrophic arthritis. Neutropenia is also observed in *ovarian dysfunction*. When the specific causes of the neutropenic state cannot be determined with the readily available clinical laboratory facilities, massive liver extract therapy⁵⁴ both by mouth and parenterally is often effective.

A clinical syndrome of polyarthritis, splenomegaly, generalized lymphadenopathy, leukopenia and anemia is known as *Felty's syndrome*⁵⁵ in adults. The proper classification of this clinical variety of arthritis remains obscure because of its relationship to endocarditis lenta,⁵⁶ disseminated lupus erythematosus⁵⁷ and the blood dyscrasias.⁵⁸

Gold Salt Therapy.—Those patients showing clinical improvement on treatment with gold salts have decreasing sedimentation rates.⁵⁹ A few cases have a preliminary transient increase in the rate. The appearance of marked leukopenia or eosinophilia is a danger signal that calls for the discontinuance of gold therapy; stippling of the red cells, as occurs in lead poisoning, may appear. Although jaundice, stomatitis and enteritis were the most common untoward reactions to gold therapy in 900 cases,⁶⁰ nine cases of purpura, one of agranulocytosis and two of severe anemia developed. Gold salts should not be used in a patient with a history of purpura or epistaxis, or until a severe anemia has been corrected.

Physical Therapy.—The application of heat to the body⁶¹ produces no significant alteration in the abnormalities of the

blood in atrophic arthritis, other than the decrease in the total leukocyte count that is associated with muscular rest and relaxation. General massage has a similar effect. An increased sedimentation rate⁶² following the application of *short wave diathermy* to questionably infected tonsils, to asymptomatic teeth showing peridontal changes on roentgen examination, and to other uncertain sites of infection has been proposed as a means of deciding on the removal of such questionable focal infections. Aggravation of arthritic or neuritic symptoms following the application of short wave diathermy to parts of the body containing unrecognized infections is an occasional unfortunate result from this energetic form of heating.

Focal Infections.—Active focal infections should be treated conservatively until the clinical activity of rheumatoid arthritis or rheumatic fever subsides and until the nonfilament neutrophil count and the sedimentation rate have returned to normal. However, since the removal of definite focal infections is most beneficial when carried out early⁴⁹ in the course of acute cases of atrophic arthritis, eradication of unquestioned infections should not be postponed too long. If the rheumatoid syndrome has subsided clinically, such an infection may account for a persisting increase in the sedimentation rate. The sedimentation rate frequently returns to normal within a week after the operation in such patients.⁶³

Vaccine Therapy.—With foreign protein shock therapy that produces a severe febrile reaction, there is a sharp drop in the leukocyte count during the first hours, followed by a leukocytosis with an increase in the neutrophils, the nonfilamented forms and the eosinophils. The sedimentation rate likewise increases. Hicks and Wyatt⁶⁴ have observed leukopenia in atrophic arthritics after intravenous injections of streptococcus protein in *minimal* doses that do not produce febrile responses. In normal individuals and in patients with hypertrophic arthritis, a significant increase in leukocytes occurred. With staphylococcus or typhoid protein in similar minimal doses the rheumatoid group showed the same increase in the white blood cell count as the normal people. After a period of months of intravenous injections of these small doses of streptococcus protein, the leukopenic response decreased markedly in these patients. Breuer¹¹ has commented on the immediate, temporary relief of joint pain and tenderness following such subreaction doses of streptococcus vaccine in rheumatoid arthritis.

SUMMARY

Alterations in the cytology and chemistry of the blood aid in the differential diagnosis of the several types of arthritis. An increase in the sedimentation rate and the nonfilamented neutrophil count distinguishes atrophic arthritis, rheumatic fever and gonorrheal arthritis from hypertrophic arthritis. Elevation of the blood uric acid during the clinical exacerbation of gout and the complement fixation test for gonorrheal arthritis are specific tests. In atrophic arthritis the streptococcal agglutinin titer is high and in rheumatic fever the anti-streptolysin titer is increased.

These alterations in the blood aid in following the course of the disease and in its therapeutic management. Measures directed at correction of the anemia, leukopenia, low serum albumin level, decreased glucose tolerance, bacterial and food allergy, abnormal purine metabolism and vitamin deficiency are of great value in the treatment of these chronic diseases.

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FIBROSITIS

FIBROSITIS is a rheumatoid disorder characterized by a nonsuppurative, inflammatory reaction in the white fibrous connective tissue, anywhere in the body, with a swelling and proliferation of the fibrous tissue in response to chilling, toxic influences (both bacterial and metabolic), trauma, or fatigue. Acutely tender fibrous bands and nodules frequently form in the muscles, tendons, ligaments, fasciae, periosteum, joint capsules and nerve sheaths, and press on arterioles and nerve filaments, causing muscle spasm and secondary pressure effects. Hence the manifestations of this disease are really protean. However, *stiffness* and *varying degrees of disability and pain*, which is increased by active motion, are always present. Fibrositis may have an acute or subacute onset, produce minimal systemic reactions, and result in complete recovery; or it may have a tendency to recur and become chronic, with prolonged pain and stiffness.

This form of rheumatoid disability is often classed under the *myositides* or inflammations of muscle in general, or under *muscular rheumatism* or myalgia, but "fibrositis" is a more accurate term because the pathologic changes occur primarily in the white fibrous connective tissue of the body. The interstitial muscle tissue is involved, rather than the muscle parenchyma, and hence muscular rheumatism should not be classed under the myositides. True myositis is relatively rare, while fibrositis has been called the commonest ailment to which human flesh is heir. "Nonarticular rheumatism" has been suggested as a better term.

Incidence.—Fibrositis, under which heading have been grouped various pathologic conditions of doubtful origin such as *lumbago*, *wryneck*, *cephalodynia* and *pleurodynia*, has been called the commonest cause of persistent recurring pain. Certainly everyone suffers more or less disability and pain in

the form of a stiff neck, backache or sore leg muscles after unusual exercise, exertion or chilling, some time or other during his lifetime.

Fibrositis is rare in the early decades of life. The chronic form becomes increasingly frequent later in life, because one attack predisposes to another. There is a definite *seasonal* incidence of this disease.

According to the British Ministry of Health Reports, fibrositis is found in 60 per cent of all rheumatic patients. Unlike arthritis, fibrositis occurs more frequently among men than women, perhaps because men are more vigorous in exertion and more apt to disregard chilling after muscular activity. Stevenson found the disease common among London busmen.

Classification.—Fibrositis is no more one disease than is arthritis, but it may be classified in two ways, either *etiologically*, or *anatomically*. Etiologically fibrositis may be primary or secondary. *Primary fibrositis* is of unknown origin and is unaccompanied by, and entirely independent of, any other recognized disease. *Secondary fibrositis* is incidental to some general infection, known cause, or dominant primary condition such as gonorrhea, rheumatic fever, influenza, atrophic arthritis, hypertrophic arthritis, tuberculosis, syphilis, trauma, or chronic intoxication such as results from gout, plumbism or alcoholism. Secondary fibrositis is especially common in cases of gout and gonorrhea where the muscles may be involved, but more often the muscle tendons are affected, especially the Achilles tendons.

Etiology.—There is no one specific causative agent. The chief precipitating factor, however, is *chilling* after exposure to cold, dampness or barometric changes, especially during perspiration after overwork or overuse of muscles in exercise, sport or in one's occupation. *Muscle strain*, either by acute trauma or from a lack of proper muscle balance due to flat feet or poor posture and prolonged overexertion in work or certain sports, may be another precipitating factor. *Toxic influences*, either *bacterial* or *metabolic*, play an important etiologic role. Gordon suggests that a *virus* may be involved in the production of fibrositis. The dysfunctioning or *irritable colon* may permit an accumulation of intestinal toxins. Faulty metabolism results from impaired circulation and faulty elimination.

The similarity of the symptoms of fibrositis to the aching stiffness resulting from muscular exertion is too close to be

overlooked. Certainly the role of *lactic acid* and other muscular tissue metabolites in fibrositis should be investigated to prove or disprove this theory. Halliday suggests that *emotional reactions* may be involved in the vasomotor imbalance, and cites illustrative cases showing how certain rheumatic symptoms have symbolic psychologic connotations. An *allergic factor* may be operative, with sensitization of fibrous tissue to some protein toxin of metabolic or bacterial origin. Abel and his co-workers found a considerable number of patients who gave positive tests for cold sensitivity.

Pathology.—Pathologic data are meager because biopsy is rarely possible, owing to the patients' strenuous objections to it, and, when it is possible, the sections are often microscopically negative. The essential inflammatory lesions, when discovered, however, occur in the white fibrous connective tissue of the body.

Llewellyn and Jones in 1915 described *two stages*, the first being an early *acute stage of effusion with a serofibrinous, noncellular, localized, inflammatory exudate*, causing a puffy swelling or edema of the tissue involved. In some cases there was an extravasation of red blood cells between the tissues from some of the capillaries, which were dilated, and a migration of leukocytes to the connective tissue between the muscle fibers.

Biopsies at the Abington Memorial Hospital Arthritis Clinic have all been in cases of secondary fibrositis, and the pathologic picture was that so typical of the subcutaneous nodules of atrophic arthritis. Indurations are found more frequently than nodules. Mallory's connective-tissue stain should be used to bring out pathologic details.

Laboratory Findings.—The laboratory findings are usually all "normal," especially the *sedimentation rate* of erythrocytes which is characteristically rapid in most cases of atrophic arthritis. Occasionally there is a slight *anemia*, but it is never so severe as in most cases of atrophic arthritis. *Arneth counts* were found by Gibson to be essentially normal. The *protein fractions, calcium, phosphorus* and *hemoglobin* are all usually within normal limits. In very acute cases there may be a slight leukocytosis at times with a slightly increased sedimentation time, but this is rare. Cultures of the nodules or of biopsy material are always sterile. α -Ray studies are likewise normal.

Symptoms and Signs.—*Pain* is the predominant symptom. It may be sharp, stabbing and constant; or merely a

dull ache, becoming severe only on movement or on assuming certain positions. Aching, soreness, stiffness, pain (which is increased by active motion) and limitation of motion often appear abruptly in any area where fibrous tissue is present but most often in muscles or around joints.

The *onset* and *course* of the disease may be *acute*, *subacute* or *chronic*. Patients often present as their chief complaint pain and stiffness in or about their joints, with no external evidence of joint pathology, such as swelling, fluid, redness, deformity or muscular atrophy.

There are few or no objective changes except tender, palpable *indurations* and *nodules*, and *muscular spasm*. These nodules occur most often at the sites where chilling and strain are most frequent. Patients at the Abington Memorial Hospital Arthritis Clinic present nodules much less frequently than those described by the English writers and Krusen. Areas of induration and muscular spasm are found much more frequently than nodules in our experience. Biopsies have been permitted only by patients with secondary fibrositis and these nodules showed histologically the granulomatous changes suggestive of the nodules of atrophic arthritis and not the fibrotic tissue, characteristic of fibrositic nodules.

INTRAMUSCULAR FIBROSITIS.—This may be *diffuse* or *generalized*, as in muscular rheumatism, or it may be *localized*, affecting only the insertion of a muscle or the fibrous sheaths surrounding the muscle bundles. The parenchyma of the muscle is not involved but only the interstitial tissue. The stiffness is due to a "jelling phenomenon" which causes whatever limitation of motion there is. Pain is localized, not at the joints but between them. This condition is often called "myalgia" or "myofascitis."

1. *Indurative Headaches (Myalgia Capitis)*.—Cephalalgia, or cephalodynia, is fibrositis of the muscles and tendons of the scalp and neck.

2. *Acute Wryneck (Acute Torticollis)*.—Stiff neck, or cervical myalgia, is a fibrositis involving the sternocleidomastoid and occasionally the trapezius muscles.

Stiffness of the neck and pain on extremes of motion occur in various diseases, with a grave or trivial significance. *Never assume that the condition is a trivial fibrositis without a thorough investigation.*

3. *Pleurodynia, Intercostal Fibrositis, Intercostal Myalgia*.—This is a fibrositis of the chest muscles, usually the intercostals, and at times the pectorals and serratus magnus.

4. *Abdominal Fibrositis*.—Abdominal fibrositis with involvement of the rectus and other abdominal muscles is characterized by pain (often very severe), tenderness (even to "fingertip pressure"), and tender spots and nodules, either single or multiple, in areas not usually affected by visceral disease.

5. *Scapulodynia* is a fibrositis of the scapular muscles, often limiting shoulder motion.

6. *Dorsodynia* is a fibrositis of the dorsal muscles of the back. It has also been called "myalgia dorsalis."

7. *Lumbago* (*spinal fibrositis*, or *myofascitis*) affects the muscles of the lower back, especially the lumbar muscles. Gordon regards it as the most common rheumatic affection of the spine, and Albee as the commonest cause of pain low in the back, where there are so many fascial and ligamentous insertions into bone. Sydenham (1624-89) described lumbago as "the third variety of rheumatism." Lumbago occurs most often in male adults, with a sudden onset after chilling, or severe muscular strain involving lifting or bending.

Only after every other possible cause of lumbar pain has been excluded, is it possible to make a diagnosis of lumbago. A careful history, a thorough physical examination and x-ray study are essential in this exclusion.

PERIARTICULAR FIBROSITIS.—Periarticular fibrositis, or capsulitis, is a fibrositis of the fibrous tissue of the articular capsule and its surrounding ligaments.

BURSAL FIBROSITIS.—Bursal fibrositis, or bursitis, is common, but it must be distinguished from bursitis which is accompanied by an increase of fluid in the bursal sac. It lacks the definite limitation of motion of true bursitis. Pain is present only on extremes of motion in the shoulder, especially abduction and internal rotation are painful, and tenderness is frequently absent. Calcification is rare.

PERINEURAL FIBROSITIS.—Perineural fibrositis, or interstitial neuritis, may cause brachial neuralgia, trifacial neuralgia, intercostal neuralgia and sciatic neuralgia. The sheath of the sciatic nerve is most often affected, and in men more often than in women.

Most of the diseases mentioned in the differential diagnosis of lumbago must also be excluded in diagnosing *sciatic fibrositis*.

TENDINOUS FIBROSITIS OR TENDINITIS.—This is an uncommon condition which involves the fibrous tissue of the tendons, fasciae and aponeuroses. The palmar fascia or apo-

neurosis is involved in Dupuytren's or in a Dupuytren-like contracture in which dense fibrous bands stand out in the palm of the hand.

PANNICULITIS.—Panniculitis, fibrositis of the subcutaneous fibro-areolar and adipose tissue, is characterized by a loss of the elasticity of the skin, which becomes more adherent to the underlying connective tissue.

Differential Diagnosis.—The *tender spots, nodes* and *fibrous thickenings, or indurations*, are the signposts of the disease.

DIFFERENTIAL DIAGNOSIS

	<i>Periarticular Fibrositis</i>	<i>Atrophic Arthritis</i>
1. Involvement.....	1. Limited to one or more definite areas.	1. Usually polyarticular.
2. Joint pain.....	2. Periarticular.	2. Definitely in the joint.
3. Joint swelling.....	3. No synovial exudate.	3. Synovial exudate very frequently present.
4. Joint tenderness....	4. Variable—absent or mild and fleeting.	4. Often marked.
5. Joint stiffness.....	5. Subjective, often first symptom. "Jelling" phenomenon disappears quickly after exercise. Freely movable after years of fibrositis.	5. Objective and subjective. Worse after exercise. Motion often limited.
6. Effect of rest.....	6. Made worse.	6. Improvement.
7. Effect of exercise..	7. Less pain and stiffness.	7. More pain and stiffness.
8. Muscular atrophy...	8. Rare.	8. Common.
9. Remission.....	9. Frequent.	9. Uncommon.
10. Systemic manifestations.....	10. Usually none.	10. Fever, hypotension, loss of weight, anorexia.
11. Anemia.....	11. Rare.	11. Common.
12. Sedimentation rate..	12. Normal—only rarely elevated.	12. Usually markedly elevated.
13. x-Ray study.....	13. No bony changes.	13. Characteristic bony changes in 85 per cent of cases.
14. Nodules.....	14. Fibrous changes.	14. Characteristic inflammatory changes.
15. Fatigue.....	15. Common.	15. Usually present.
16. Nervous exhaustion..	16. Common.	16. Usually present.
17. Prognosis.....	17. Good; recurrence frequent.	17. Uncertain.
18. Response to therapy	18. Variable—occasionally very prompt.	18. Always rather slow.

Similar attacks may have been suffered by the patient previously.

The fibrositis is worse after rest, better after gentle, mild exercise; in contrast to the arthritic, who feels better after

resting and worse after exercise. Furthermore, fibrositis is readily differentiated from even early atrophic arthritis by the characteristic and persistent negativity of clinical laboratory and x-ray evidence of constitutional reaction, or of intra-articular disease.

The diagnosis of fibrositis depends largely upon *exclusion*. A careful history and a completely thorough physical examination, along with laboratory and x-ray studies are essential to correct diagnosis and proper determination of all etiologic factors in every case.

Prognosis.—Fibrositis is the most tractable of all the rheumatic affections. Its prognosis is very good, especially in cases of acute onset, where rapid cure is practically the rule. While acute attacks of primary fibrositis usually last a few days or weeks, they often recur. Chronic cases require longer and more persistent treatment. The chronic forms may persist for years, but the patients are usually able to continue their work with only slight inconvenience. There is rarely enough contracture of fibrous tissue to limit joint motion permanently, even in periarticular fibrositis, unless it involves the shoulder. If systematic shoulder exercises are not practiced faithfully, shoulder motion may be limited. Similarly, in primary fibrositis of the palmar fascia, a Dupuytren's contracture may result unless the same precautions are taken.

Most patients with either acute or chronic primary fibrositis are relieved by treatment. However, recurrence is common, for one attack seems to predispose a patient to another. Indeed, relapse is said by Copeman to be ultimately almost certain unless the fibrous nodules are thoroughly broken up and completely resolved.

The prognosis, of course, depends upon the *etiologic* factors involved and the ability to remove these factors. Careful elimination of all etiologic agents and persistent use of all available therapeutic resources are often necessary to obtain favorable results.

TREATMENT

An exact *etiologic diagnosis* is an absolute prerequisite to adequate, rational therapy. Every etiologic factor operative in a given case must be determined and eliminated if possible. Careful study is necessary to detect *postural defects*, *focal infection* and *gastro-intestinal derangements*, both anatomic and functional. The *mode of living* and *daily habits* must be

investigated, especially in respect to working, resting, sleeping, exercising, eating, drinking and smoking. Mental and physical *fatigue* and *exhaustion* must be avoided. A balanced regimen, with regular rest and exercise, is a safeguard against repeated attacks of fibrositis in people subject to it. *Rest*, *physiotherapy* and the *elimination of focal infection* are the three most effective therapeutic agents. To rely only on any one particular method of treatment is to invite failure.

REST.—During the acute stage rest is very valuable. *Rest in bed* relaxes the muscles, protects the patient from chilling, and hastens recovery. It should be prolonged as long as the patient's condition warrants. If bed rest is impossible or refused by the patient, *localized rest* of the affected part, with two periods of bed rest for an hour or two in the middle of the morning and the middle of the afternoon, may be substituted.

DRUGS TO RELIEVE PAIN.—*Phenacetin* and *aspirin* (aa. gr. v, q. 3h.) are usually effectual in alleviating the pain; or *sodium salicylate* and *calcium gluconate* (aa. gr. xv, q. 3h.) may be tried. If the pain is very severe or agonizing, *Dover's powder* or *codeine sulfate* may have to be added to the above medication temporarily. A *saline aperient* should be given to open the bowels freely. Fluids must be forced so that a minimum of 2,500 to 3,000 cc. of water and fruit juices is taken daily.

HEAT.—Heat in any form is very effective in relieving symptoms. It is most easily supplied by an *infra-red lamp*, *electric baker*, or an *ordinary electric heater* for an hour (q.i.d.); or, if these are unavailable, by an *electric hot pad*, *hot salt* or *sand bags* or *hot baths*.

COUNTERIRRITATION.—Counterirritation by means of *poultices*, *mustard plasters*, *capsicum* or *belladonna plasters*, *acupuncture*, or *daily dry cupping* over the tender area, helps to control pain.

MASSAGE.—After the acute stage of effusion is over and the pain is controlled, progressively deeper and firmer massage should be started. Though light at first, massage should be made as vigorous, *gradually*, as the patient can tolerate it, to completely break up the fibrous nodules and cords, for unless they are destroyed "relapse is ultimately almost certain." Massage always should be *preceded* by heat, supplied by infrared radiation, diathermy, or short wave diathermy. *Firm massage*, *kneading* and *deep friction* may cause a transitory increase in pain for several hours after

treatment, but in from two to ten days definite improvement is often noticed.

EXERCISE.—Even mild trauma must be avoided lest the lesion be aggravated, but *gentle exercise* for the involved part should be begun as soon as possible.

NEEDLING.—Whenever the pain can be localized to definite spots or nodules, simple “needling” or the injection of 5, 10 or 30 cc., as needed considering the anatomy of the area involved, of sterile 2 per cent procaine hydrochloride solution every day or two, may relieve the pain.

HISTAMINE AND IONTOPHORESIS.—Histamine is of special value in cases of widespread fibrositis, with poor peripheral circulation, and extreme stiffness on awakening in the morning. Histamine acid phosphate is injected hypodermically, starting with 0.1 mg. and increasing the dose by 0.05 mg. daily until improvement results, usually requiring a dose of 0.3 to 0.5 mg. This dose is then continued every two or three days, or increased if the response decreases.

After each injection the patient must *lie down for half an hour*, or longer, because of the resulting dizziness, thumping headache, and flushing of the head and neck.

Iontophoresis, ionization or cataphoresis for ten or fifteen minutes can be employed, using *histamine, mecholyl*, 2 per cent *lithium iodide* or 2 per cent *sodium salicylate* solution. To introduce these drugs into the tissue by using galvanic current is of value, especially during the acute stages. MacKenna claims that it produces a complete cure.

Vitamin B₁.—To correct any deficiency in *vitamin B₁*, *thiamin hydrochloride* (600 units t.i.d. per os, or 10,000 to 20,000, or even 30,000 units a day by intramuscular, or intravenous injection) should be given. Some patients seem to respond better on intramuscular injection of the whole vitamin B complex instead of only B₁.

Foci of Infection.—These should be sought for diligently and eliminated.

Prevention.—The ultimate aim of treatment is prevention; or, failing in this, to secure arrest of the process as soon as possible. Prophylactic measures are therefore essential. All predisposing factors should be given proper attention during convalescence.

The patient must be protected against *respiratory infections, chilling, dampness and sudden changes in temperature*. Burt warns against the trauma and chilling caused by wearing heavy coats and clothing outside, and totally backless

evening gowns inside the house. While these patients should be warmly clothed, the material should be light in weight, for heavy coats and clothing, with consequent trauma, may cause recurrence of fibrositis of the neck and shoulders. Mental and physical fatigue must be avoided. While adequate exercise gradually instituted is important, a happy medium between the proper amount of exercise and exercise that fatigues, must be sought in each case. Occupational causes of fibrositis should be remedied.

The *general health* should be built up by fresh air, sunshine, proper diet, adequate bed rest and relaxation. There is some evidence that excessive use of tobacco and alcohol predisposes to relapse.

Postural defects must be corrected by systematic, active postural exercises. Obesity is to be avoided. Attention should be given to the feet, and correct shoes prescribed, so that all defects in physical balance are corrected. All of these measures are as necessary as is the readjustment of the dietary, endocrine and autonomic balance.

As cold and dampness militate against recovery, it may be advisable to have the patient go to warm, dry, pleasant and equable surroundings. A complete *change of environment* relieves the patient, also, of the stress and strain of his everyday life.

If the above regimen does not result in cure, the treatment used in atrophic arthritis should be instituted. Indeed, every case of fibrositis *should be suspected* of having a rheumatic basis, and should be carefully analyzed to determine the presence of any of the etiologic factors known to be operative in the rheumatoid syndrome.

SUMMARY AND CONCLUSIONS

Fibrositis is a definite rheumatoid disorder, a distinct disease entity, "practically unrecognized in America (because) American clinicians have been loath to recognize (it) since its supposed pathology is so ill defined, its symptomatology so subjective, and its chemical reactions so 'normal.'"

It probably is more common than is realized. It is rare early in life, but common in the middle, and especially the late, decades of life.

Etiologic factors include chilling, muscular strain, toxic influences (both bacterial and metabolic), trauma, fatigue and dietary imbalance.

Pathologic changes occur in the white fibrous connective

tissue of the body—in an acute stage of effusion with a sero-fibrinous exudate, and a later stage of organization with fibrous nodules, cords and indurations.

Laboratory and x-ray findings are all normal.

Pain and stiffness, worse after rest and better after mild exercise, and easy fatigue, are the symptoms of primary fibrositis. To these are added in secondary fibrositis, the symptoms of the primary underlying disease.

Patients appear to be in robust good health with no systemic manifestations and no objective findings except tender, palpable indurations, nodules and cords with an associated muscular spasm.

The fibrous thickenings, indurations, nodules, cords and bands are the sign-posts of fibrositis.

Rest, physiotherapy and the elimination of focal infection form a therapeutic triad to which many of the other measures described may have to be added to achieve a cure.

The prognosis is good, although one attack predisposes to another one.

Myositis, myalgia, arthralgia and neuralgia should never be used as synonymous with fibrositis, although such usage is current in medical literature today. "Nonarticular rheumatism" has been suggested as a better term than "fibrositis."



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METABOLIC AND DIETETIC CONSIDERATIONS IN THE TREATMENT OF ARTHRITIS

Introduction.—The role attributed to nutritive factors in the pathogenesis, symptomatology and therapy of arthritis is often exaggerated or minimized. On one hand, the role of nutritional factors is emphasized far beyond its appropriate sphere of influence, and bizarre dietary measures based upon doubtful premises are exploited in certain uncritical quarters. On the other hand, consideration of nutritional factors is summarily dismissed in some quarters merely because there is no clear-cut evidence that any single nutritional deficit or excess is responsible for the complete clinical pattern of any of the major syndromes of arthritis. The view, however, that considerations of nutrition can be dismissed because of recognized limitations is dependent upon the erroneous assumption that such factors must play either an exclusive role or none at all.

Many clinical conditions, particularly the chronic arthritides, are complicated if not characterized by subclinical manifestations which appear in the disease entities *xerophthalmia*, *beri-beri*, *scurvy*, *rickets* and *pellagra*, now universally regarded as deficiency syndromes. It is reasonable to suspect that such features, when presented by arthritics, arise as results of *minor degrees* of corresponding nutritional deficiencies.

In addition to individual vitamin deficiencies which may complicate an arthritic condition, other kinds of nutritional disturbances may be present. These may be *secondary results* of the increased demands or decreased capacity for absorption and utilization of certain foodstuffs incidental to the arthritic state.

In order to obtain the maximum benefits which can be realized by dietetic control or management it is essential to

check each patient with respect to symptoms which may have an origin in dietary imbalance, special nutritive requirements and capacities, adjusting the diet in the several particulars indicated by individual analysis. It is therefore the purpose of this discussion to direct attention to both the *singular* and *collective* role of nutritional factors in respect to some of the deviations encountered among arthritics and to indicate, in the light of available information, the *general* and *specific* therapeutic implications to be derived therefrom.

GENERAL ROLE OF NUTRITION

Nutrition in the broad sense includes more than is suggested by diet, which refers to materials ingested. Nutrition involves the maintenance of the tissue cells in a medium suitable for their growth, development, and for their functional maintenance and repair. There are several recognized levels of nutrition; viz., *inadequate*, *adequate* and *optimal*. The aim of any therapeutic regimen is the achievement of optimal nutrition. The presence of infection, vascular defects and other conditions of a similar nature often existing in the arthritic, imposes further limits upon the extent to which a given supply of dietary materials may meet the nutritional needs of the colonies of cells comprising tissues and organs. The presence of *infection* exerts both a direct and indirect influence upon cells and modifies the amounts of materials required for the maintenance of normal or optimal function. During periods of fever, the total metabolic interchange is increased over the basal afebrile level, so that materials of fixed tissues are consumed unless sufficient calories are provided from outside sources.

Optimal nutrition requires more than the simple provision of certain quantities of various substances; it demands that these materials be provided *under circumstances most favorable for their utilization*. This involves attention to the presence of infection, to the physical and physiologic activity of the organism as a whole, and to the balance of the several foodstuffs. In treating the subjects of such deficiencies one should, according to Spies, "... insist upon as little activity as possible on the part of the patient until the repairs to affected tissues are under way. In many cases lesions heal following rest in bed. Even when the diet remains inadequate there is a significant increase in the blood concentration of the coenzymes if the patients remain at rest in bed." Furthermore, there should be a *balance* of various nutritional factors,

as emphasized by Elvehjem regarding the use of nicotinic acid in pellagra: "The full value of one factor can only be realized when it is used in conjunction with all the essential factors. . . . Nicotinic acid is much more effective when all other factors are supplied in optimum amounts."

CALORIC VALUE

For the patient who is *essentially normal in weight*, a caloric supply providing maintenance is generally indicated. In view of the fact that the patient is usually required to remain in bed during the active stages of the disease, a diet providing about a 10 per cent excess over the basal energy expenditure is generally sufficient. Such an amount is adequate to cover the daily losses and at the same time does not impose any physiologic burdens upon the patient in terms of unnecessary exogenous metabolic activities.

The patient who is *grossly underweight* naturally requires foodstuffs providing a supply of calories in excess of the quantity actually used during the course of the day. Not only must the basal needs be covered but, in addition, a quantity provided which can restore reserves. The underweight individual not only needs an excess of calories in order to restore tissue substance, but he also requires a quantitative excess of the specific materials used. A diet providing merely an overabundance of calories is not necessarily optimal for the underweight individual. It is both theoretically and empirically necessary to provide liberal amounts of *all* of the known essential food factors. This requires emphasis upon qualitatively good proteins and vitamins.

When, however, the patient is *grossly overweight* and it is desirable to induce a general weight reduction in order to diminish the traumata to weight-bearing joints, it is necessary to lower the level of the caloric intake below the amount required for maintenance. When a reducing regimen is undertaken, care is exercised to provide a little more than the average proportion of protein and to supply sufficient accessory substances, usually in the form of a fairly bulky diet. The first provision tends to augment the rate of metabolism due to the specific dynamic action of protein and, coincidentally, to favor losses of body water.

In appropriately selected cases, marked clinical improvement in terms of soft tissue swelling, pain and decreased mobility may follow sharp *curtailment* of the caloric supply to a submaintenance level. This may be true even in instances

wherein the coincidental vitamin intake is minimal. Such periods of temporary diminution of the severity of symptoms may be observed among stabilized patients with atrophic arthritis. The nature of the clinical benefit is related in part to the loss of surfeits of body water and other tissue "detritus." While a therapeutic regimen of this kind cannot be applied for extended periods, the same kind of influence may be obtained by an adjustment of the distribution of the calories provided by major foodstuffs wherein the carbohydrate fraction is adjusted to a comparatively low level.

The caloric value of the diet is therefore estimated with regard to the *individual* requirement and not determined by reference to the clinical type alone. Thus the calories are prescribed to meet the actual needs of the patient in terms of the optimal energy balance.

COMPONENTS OF THE ARTHRITIC DIET

Protein.—The fact that the proteins of the diet provide the amino-acids or structural units, of which the framework of tissues is constructed, suggests that proteins of good biologic quality should be liberally provided in the diet of patients whose disorders are characterized by wasting or atrophic manifestations. The moderate tendency toward a low-grade peripheral edema in certain patients is associated with moderate reductions in the level of serum albumin. While this may be due to a defect in the mechanism whereby albumin is produced, resulting from chronic infection, it is nevertheless clear that a *liberal supply* of the raw materials from which albumin is elaborated should be provided.

There is a general impression that the arthritic suffers from *toxemia*. Among the lines of evidence cited to support this view is the fact that the fingernails of arthritics are sometimes malformed, brittle and low in cystine. It is believed that this defect is due to a diversion of cystine, a sulfur-containing amino-acid, from its structural use to a detoxifying function. A *protective* influence of protein in the diet against certain toxic agents is indicated by Meyer. Experimental animals are protected against otherwise lethal doses of phenol and of diphtheria toxin by diets high in protein. According to O'Neal indoluria is frequent among patients with chronic arthritis and constitutes evidence of incomplete detoxification. The ingestion of a high protein diet eliminates the indoluria. In view of these considerations, as well as the well-known role of glyco-

coll in detoxifying benzoic acid, it is evident that the derivatives of proteins play an extensive role in the defense of the organism against a variety of noxious organic materials.

Attempts made in this laboratory to produce gross articular pathology in rats by feeding diets inadequate in the amino-acids, cystine and lysine, and by rations in which the incomplete protein gelatin provided the nitrogenous fraction, were negative. While these preliminary experiments do not exclude the possibility that certain deficiencies of amino-acids may be significant in the pathogenesis of some phases of the arthritic syndrome, they suggest that the clinical pattern is not based upon the aforementioned deficiencies alone.

Restrictions of *nucleoproteins* are sometimes considered to be necessary for persons with rheumatic disorders, particularly for patients with *gout*. However desirable this may be for the gouty subject there is no basis for the restriction of red meats, liver and glandular foods to the arthritic.

The protein supply should be provided from a number of biologic sources in order to insure not only a *variety* in taste, but an *adequacy* of amino-acid composition. The latter requirement can be met by the liberal use of *meats*, *dairy products* and *eggs*. No particular variety of protein from any source is known to be generally contra-indicated. The *total protein* should amount to at least 1 gm. per kilogram of body weight.

Carbohydrate.—Wide differences of opinion are expressed in regard to the proper level of carbohydrate in the diet for the arthritic. Thus, on the one hand, it is stated that the arthritic can tolerate a *high* carbohydrate diet; and, on the other, that the arthritic fares better on diets *low* in concentrated carbohydrate foodstuffs. In support of the former view the normal respiratory quotient of arthritics is cited as evidence of a normal capacity to metabolize carbohydrates and furthermore the ingestion of rations high in carbohydrates does not always induce exacerbations of the disease. On the other hand, attention is directed to the delayed rate of removal of ingested glucose from the blood of many arthritics. It is further alleged that patients do better when the concentrated carbohydrates of the diet are kept at minimum levels.

These apparently contradictory views can be harmonized by recognizing that carbohydrates are *not toxic per se*, and that the benefits of carbohydrate restriction when present are related to certain *limited but definite* factors.

One of the general empirical reasons for restriction of

concentrated carbohydrates relates to the relatively low amounts of accessory substances or vitamins in foodstuffs of this kind. Since the supply of vitamin B is often barely minimal under ordinary conditions, the available supply may be made *relatively inadequate* by excessively high carbohydrate ingestion. Another relevant consideration relates to the influence of carbohydrates upon the management of the low-grade *edema* presented by some chronic arthritics. Carbohydrates, when stored as such, hold considerable portions of water, and limitation of glucose favors a state of relative dehydration. The influence of the solute sodium chloride in holding tissue water is well recognized; the comparable role of the solute glucose is less widely appreciated. The control of the edema of the chronic arthritic can be considerably influenced by regulation of this latter factor.

Exclusive of the aforementioned instances, a supply of *one-third* to *one-half* of the calories (exclusive of that provided by protein) in the form of carbohydrate is empirically desirable. No specific kind of dietary carbohydrate is known to be contraindicated for the rheumatic.

Fat.—The quantity of *fat* in the diet bears in general a *reciprocal* relation to the amount of *carbohydrate* in the ration. The reasons for including a comparatively large amount of fat, as compared with that usually provided by the usual dietary, is to "spare" vitamin B and to minimize the accumulation of tissue water by maintaining metabolic conditions favorable to the elimination of water. In the selection of the kinds of fat to be included, those rich in the fat-soluble vitamins should be considered, not only because of their known vitamin content, but because of other associated special nutritive qualities, *i. e.*, essential unsaturated fatty acids.

There is some evidence to suggest that fats, as well as proteins, may afford certain *protective* qualities toward noxious agents. Fats might be expected to further augment the defensive qualities conferred by the already recommended relatively large amount of proteins.

While patients with hypertrophic arthritis as a class show a higher level of cholesterol in the blood than do normal patients with atrophic arthritis, this does not necessarily indicate that fats should be reduced to a minimum.

Except for those persons who have an intolerance to fatty foods based upon gastro-intestinal dysfunction or the existence of a gouty diathesis, there are but few instances wherein unusual limitation of fat is indicated among arthritic subjects.

The fats should therefore make up about *one-third to one-half* of the caloric value of the diet, exclusive of that provided by protein.

Vitamin A.—Gross deficiency of Vitamin A is not conspicuous among arthritic subjects. However, there are a few symptoms encountered with some frequency which may have an origin partly upon such a nutritional basis.

Frequent *upper respiratory infections*, indicative of an unusual susceptibility, while by no means pathognomonic, in some instances may be due to deficiency of Vitamin A. The moderate and sometimes profound *disturbances in liver function* evident in the more acute manifestations of atrophic arthritis and the recognized interference of this with the capacity to transform provitamin A into the active vitamin suggest the desirability of providing very liberal amounts of the preformed substance.

Any widespread evidence of disturbances in the epithelial tissues may be regarded as suggestive of evidence of Vitamin A deficiency. A therapeutic trial is the best and final means of determining whether any of the abnormalities actually arise upon a nutritive basis.

The *basal diet* of the arthritic should include at least 6000 International Units of Vitamin A and, if any features of severe deficiency are present, this should be supplemented with 20,000 to 50,000 units per day as a therapeutic dose.

Vitamin B.—As indicated in the section on the carbohydrates, symptoms suggestive of Vitamin B deficiencies are frequently encountered.

With respect to *B₁* or *thiamin*, the full syndrome of beriberi does not appear in arthritis. Furthermore, while beriberi is often accompanied by joint pain (arthralgia), true arthritis is not a common complication. However, several symptoms conceivably resting upon a basis of such deficiency do occur among chronic arthritics. *Anorexia* or lack of appetite is a frequent complaint. A *peripheral neuritis* is sometimes present, together with an occasional inability to dispose properly of ingested carbohydrate. The low-grade *peripheral edema* already referred to may be similar in origin to that of the so-called "wet beriberi."

The *basal ration* for the arthritic should include at least 250 International Units of thiamin, equivalent to 1 mg. of thiamin. If deficiency symptoms or subclinical manifestations are conspicuous, therapeutic doses up to 20 mg. of thiamin per day are justifiable.

Vitamin C.—The *scorbutic state* in its fully developed form is fortunately rare. The syndrome responds favorably to the administration of adequate doses of cevitic acid.

There are several other clinical states within the class of rheumatoid diseases which show many features of the scorbutic state in a mild form: The generalized *connective tissue weakness*, that is, a decrease in the integrity of the intercellular cement substance, is often notable. One site where the consequences of this situation may be recognized by clinical inspection is the *gums*. The gingivae of arthritics are frequently tender, spongy or swollen and infected. Some patients in the rheumatoid group, although by no means all, show evidence of *decreased capillary strength*, evident clinically by an increased tendency to bruising or by one of the several procedures for estimating rupture level of the cutaneous capillaries. *Muscular tenderness* and *weakness* is another frequent feature of the arthritic which may have an origin in a deficiency of cevitic acid.

It is well recognized that *infectious conditions* are associated with increased demands for cevitic acid, so that patients present abnormally low levels of this material in the blood even in the presence of an otherwise adequate supply of cevitic acid. Infectious agents of several kinds inactivate or destroy Vitamin C. Furthermore it has been demonstrated that the administration of test doses of the material in atrophics, and particularly in atrophic spondylitics, produces lesser rises in the blood level than do the same doses in normals. Also, the renal output of cevitic acid is lower in ill arthritics than in normals. While this increased tolerance and increased demand for Vitamin C is evident among arthritics, it is not specific for or limited to this condition.

Experimental animals maintained upon a ration providing *suboptimal* supplies of this substance develop lesions which are suggestively similar to those regarded as characteristic of rheumatic fever and of atrophic arthritis. Rinehart has suggested that a deficiency of this material plays a role in the pathogenesis of the rheumatic lesions. Others deny the importance of these experimentally induced lesions with those appearing in human clinical material, partly upon differences in micropathology, partly upon the basis of the failure of large doses of cevitic acid to decrease the attack rate in rheumatic children. Despite the admitted failure of this agent to provide complete clinical protection of or arrest of the clinical process of rheumatoid disease, it is reasonable to utilize this agent

within legitimate limits. Neither this nor any other single measure should be expected to provide a complete control of the situation.

The *basal ration* should include at least 300 International Units, equivalent to 100 mg. of cevitamic acid. If additional symptoms are present, doses of cevitamic acid up to 400 mg. per day are indicated.

Vitamin D.—The syndrome of *rickets*, recognized as a deficiency disease, does not loom large among the rheumatoid disorders. However, there are some features of this deficiency syndrome which appear with some frequency and severity among arthritics.

The most conspicuous of these is *demineralization* of the skeleton in atrophic arthritis. The pathogenesis of this situation probably depends upon a change in the matrix of the bone secondary to noxious influences described in the introductory article. However, when demineralization exists, it is obvious that the conditions most favorable for mineralization are similar to those for growth.

There is a long-established and clinically justifiable practice of giving chronic arthritics whatever benefits may be inherent in the provision of extra supplies of calciferol in the form of cod liver oil. Within the past few years claims have been advanced for the therapeutic value of certain materials related to Vitamin D when administered in *extremely high dosage*. The effects are usually associated with some evidence of mild toxicity rather than with evidence of a replacement of nutritive influence.

Nicotinic Acid.—While extended attention has not been given to the role of this substance in arthritis, early studies relating to the water-soluble vitamin complex of which this is a component justify consideration of it in the light of its known physiologic qualities.

Some of the *gastro-intestinal* symptoms seen with frequency among arthritics are similar to those occurring as results of lack of this material. Furthermore, the administration of the Vitamin B complex often helps in restoring to normal the dysfunctioning gut of the chronic arthritic.

Certain other features bear a suggestive relationship to the consequences of deficiency of nicotinic acid, viz., an *anemia* and a *disturbed psychic pattern*. While other measures of a physical nature are generally applied to this connection, attention should be called to the property of nicotinic acid in augmenting peripheral blood flow, and this agent might well be more widely utilized in this connection.

Other Accessory Factors.—No claims have yet been made for the role of other accessory foodstuffs, such as *riboflavin*, *vitamins E, K, B₆*, and *P*, the *filtrate factor W*, and *pantothenic acid*. None of the recognized features of experimental syndromes based upon deficiencies of these materials appears with remarkable frequency among patients with chronic rheumatic disease.

Minerals.—Claims for the therapeutic value of mineral waters and the concentrated salts derived from mineral springs and from the ash of seaweed and other materials have been made with the implication that these substances make up deficits in the mineral supply of the ordinary dietary. Most of the alleged benefits are attributed to the pharmacologic effects as gastro-intestinal stimulants rather than to their nutritional qualities.

While the administration of *potassium iodide* is sometimes beneficial in certain cases of arthritis, the comprehensive claims advanced by pseudoscientific "experts" for the anti-rheumatic efficacy of iodine-bearing salts is not valid. There are no data indicating that such cases occur with unusual frequency in the area of the low iodine or "goiter belt" of the Midwest.

One of the most widely exploited aspects of the role of minerals in the management of chronic rheumatic disorders relates to the alleged disturbance in the *acid-base balance*. It is widely believed among the laity that the arthritic suffers from an "acid condition." On this premise of "acidosis" a diet containing an alkaline ash or a dietary supplement of an "alkalinizer" is recommended. There are, however, no generally recognized data supporting this view. It is conceivable but not proved that the low-grade edema characterizing certain stages of chronic disease might be benefited by the use of diets low in sodium. Certainly this possibility does not constitute sufficient basis for the routine administration of diets extremely low in sodium chloride.

The conspicuous skeletal atrophy of atrophic arthritis has suggested the possibility that diets should be made *high in calcium salts*. It is not necessary to conclude that the diet should be enriched by accessory supplies of this material if the basal ration is reasonably well selected.

As noted in the clinic on "The Blood in Arthritis," there is a frequent incidence of a *hypochromic anemia*. This has suggested to some the desirability of providing an extra dietary supply of iron salts. Except in cases presenting marked

evidence of deficiency, sufficient iron usually can be provided in the form of foodstuffs, including meats, eggs and vegetables.

There are no quantitative data substantiating the claims sometimes made for the special nutritional importance for the arthritic of the salts of minerals occurring in lesser amounts in the body, such as copper, manganese, magnesium, cobalt, nickel, and aluminum.

Water.—The amount of water required for the individual is usually adequately regulated by thirst. There is no clear evidence to indicate that the arthritic has special requirements in this respect.

If quantitative approximations are in order, it may be suggested that sufficient water should be ingested to provide a *renal output* of about 1500 ml. per day of a specific gravity of nearly 1.015. If the concentrating capacity of the kidneys is diminished, a larger renal output is desirable.

The retention of excessive amounts of water by the body is not so much dependent upon the ingestion of too much water, as such, as upon amounts of solutes in excess of the required quantity. Thus the control of edema in the arthritic should not be attempted by means of artificial restrictions of water but by management of solutes which tend to "hold" water.

OTHER FACTORS IN DIETETIC THERAPY

Bulk of the Diet.—*Intestinal stasis* can be overcome generally, in part at least, by the inclusion of considerable portions of indigestible bulky residues in the ration. However, there are some patients in any group of arthritics who are adversely affected by foods containing indigestible residues, since they have irritable intestinal tracts. For these persons a less bulky diet is indicated. Sometimes this latter situation requires the administration of supplementary amounts of concentrated accessory factors or vitamins.

Palatability.—Often artificially developed likes and dislikes for certain kinds of foods contribute to the development of nutritional deficiencies. The correction of improper eating habits of this sort requires more than the simple recommendation as to the needs for particular foods: it demands convincing and compelling arguments to break down long-established customs.

Not infrequently, chronically ill arthritics complain of a *lack of appetite* and no food seems palatable. Under these

circumstances optimal nutrition cannot be secured by merely presenting a well-balanced and attractive tray. Under these circumstances *supplementary administration of vitamin B* may stimulate the appetite. Bitter tonics such as *nux vomica* may be used in this connection. In *extreme cases* the administration of insulin is recommended to induce active hunger and overcome the barrier of subjective unpalatability.

Food Intolerance and Idiosyncrasy.—While individual idiosyncrasy may appear among persons with rheumatoid diseases, it occurs with no greater frequency than among persons in the general population. There is no unequivocal evidence of foods toward which arthritics as a class are either sensitive or hyperreactive in the allergic sense.

A few persons appear to be intolerant of excessive amounts of *fats* in the diet. As noted in the section of this class of foodstuffs, this is particularly evident in the patients with gout and, as might be expected, among patients with poorly functioning gallbladders. There are no sound data supporting the once-held view that arthritics are peculiarly sensitive to nucleoproteins.

SUMMARY

Many patients with arthritis show evidence of nutritional imbalance. In these and in most other arthritics convalescence and recovery may be initiated, or at least expedited, by the institution of appropriate dietetic measures.

The requirements of the sick arthritic are rarely satisfied by the provision of materials in amounts comparable to those which are adequate for the normal subject. Dietary requirements for patients may vary widely, not only from one another, but also from time to time in the same individual, depending upon the physiologic demands of activity, infection and nutritive reserve. It is therefore necessary to evaluate each individual patient with respect to the entire clinical state.

For practical purposes it is necessary to supply a *basal ration* suitably balanced with respect to the major foodstuffs and containing liberal amounts of the known essential minerals and accessory foodstuffs. Empirically this means that all arthritics should be given a diet which is calorically adequate and qualitatively balanced so that the proteins, fats and vitamins are relatively high and the carbohydrates low with respect to the proportions in the ordinary or average diet. These requirements may be satisfied in general with a diet consisting largely of meats, eggs, dairy products, and fruits

and vegetables of the 5 per cent and 10 per cent carbohydrate class.

In the presence of symptoms conceivably having an origin in dietary deficiency, additional supplements of the indicated factors should be provided in therapeutically sufficient amounts. Under ordinary circumstances the caloric value of the ration should be adjusted to cover, but not exceed, the energy output. Gross overweight and underweight should be controlled by appropriate periods of modified caloric balance coupled with due regard for the qualitative requirements for essential amino-acids and vitamins. Under limited circumstances temporary periods of submaintenance may be utilized to effect a discharge of excesses of tissue water and possibly other kinds of surfeits. Certain patients, particularly those in whom infectious factors are minimal, frequently show dramatic clinical response to this regimen.

The *cumulative* effect of modifying the several features of the disorder by means of directional dietary control, together with the other measures discussed in this symposium, will afford benefit to the majority of patients. A coordination of the various influences—dietetic, physical, mechanical, physiologic and pharmacologic—directed to the achievement of *optimal* nutrition of all tissues is requisite to, and definitive of, the most effective therapeutic management of the arthritic subject.

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FOCAL INFECTION AND ARTHRITIS

FOCAL infection and its relationship to arthritis are seriously considered by some members of the profession, but are minimized by others. Focal infection may play an important role in the rheumatoid syndrome; it may be the chief etiologic factor, it may be of secondary consideration, or it may have no relationship whatever. Its relationship as an etiologic factor must be determined by familiarity with the rheumatoid problem, by clinical experience in the handling of these patients, and by comprehensive evaluation of the analyses of experienced collaborators in the specialties.

Many clinicians advocate the early removal of contributing foci, with little regard for the general well-being of the patient. In the care of both dispensary and private patients in the arthritic service of the Abington Memorial Hospital it has been found that gradual eradication of focal infection is accomplished most effectively, following recovery from the acute attack, by means of bed rest and other therapeutic measures.

Focal Infection Defined.—The nature of focal infection and its role in the production of disease was described and emphasized by Billings in a paper presented twenty-eight years ago, in which he reported on ten cases of chronic arthritis and six cases of subacute and chronic parenchymatous nephritis. A focus of infection in each case was found in the faucial tonsils, following the removal of which recovery resulted.

There are still some clinicians who regard focal infection as unimportant. This iconoclastic view is based upon the fact that clinical recovery from systemic manifestations does not *always* follow the eradication of foci. It is assumed that

such failures negate the whole principle. This negative attitude is directed alike toward hypertrophic arthritis, which is regarded as degenerative and hence unrelated to infection, and toward atrophic arthritis, which is also regarded in these quarters as inaccessible to any influence. Rheumatologists generally appreciate the fact that removal of foci represents but *one* link in the chain of therapy. All links are important. Rarely does the removal of a single focus remove the only activator of the arthritis. Treatment of the disease begins, but does not terminate, with the conservative removal of foci of infection.

The viewpoints of outstanding clinicians interested over a period of years in the arthritic problem are presented here as reflecting mature judgment regarding focal infection:

Pemberton:⁷ "Except in early and mild cases, focal infection should be removed in arthritis only after optimal physiology has been obtained in the arthritic sufferer, following intelligent rest in bed."

Minot: "The early removal of foci is indicated but the patient should be built up before undertaking debilitating surgical procedures."

Snyder: "In rheumatoid groups in which infection is the outstanding etiologic factor, the most clearly indicated method of attack is the removal of all offending foci of infection as rapidly as the patient's condition permits, the most easily accessible foci being removed first."

Haden: "Focal infection is only an influencing factor, not the one of chief importance. Nevertheless, it is unwise to allow evident focal infections to remain. They should be removed early in mild cases; in more advanced cases, when patients are on the upgrade."

Hench: "In the face of progressive arthritis, when the building-up processes do not otherwise materialize, procrastination in removal of foci seems unwarranted and the risk thereof is justified if foci are removed in conformity with good clinical and surgical judgment."

THE ORAL CAVITY

In the analysis of arthritic cases it is customary to start with a thorough examination of the oral cavity. This region is the most frequent site of infection.

Gingival Infection.—In this study attention is therefore directed not only to the apical portions of the teeth but to the gingiva. Infection in these tissues is likely to be disseminated

to other parts of the body because of the unusually rich blood and lymphatic supply in this region. From the therapeutic standpoint, infection in the gingiva is open to control by *mechanical and chemotherapeutic measures*. When gingivitis and pocketing are present, the teeth are carefully scaled and calculus and other débris which has collected at the gingival margin are removed. Talbot's iodine may be applied to the pockets for a few seconds and the excess solution rinsed from the pockets with a 0.9 per cent solution of sodium chloride. Following this the gums are massaged by means of a rubber gum "massager." This type of therapy, usually at weekly or biweekly intervals, restores the gums to a healthy condition.

The origin of gingivitis is somewhat uncertain but restitution towards normal can best be achieved by a combined attack in which attention is directed to the general health as a whole, the removal of calculus, and the restoration of normal "physiology" in the gum tissue by improvement, through massage, of the local circulatory condition. Gingivitis may be considered a focus of infection requiring special attention when encountered in arthritis.

Infected Teeth.—There is a question as to whether a *pulpless tooth* is free from infection or whether it may become involved at some future time. Pulpless teeth showing apical disease should be removed. The retention of questionable teeth may interfere with treatment, lower the general resistance of the patient and cause disturbance elsewhere in the body, as, for instance, in the prostate. *Retained roots, erupted and unerupted third molars, alveolar infection, cysts, questionable crowns and bridges* should be critically appraised in studies for foci in the mouth. In the early stages of atrophic arthritis the removal of infection associated with teeth may give dramatic results. In advanced cases the removal of infection associated with teeth may be equally important in that it improves the patient's general condition, but it is less dramatic since it can have little effect on the already damaged joints. Even in elderly, chronically ill patients the careful removal of infection associated with the teeth is advisable, as soon as the patient's condition warrants it. After all known foci are cared for and clinical results still suggest an influence from some focal infection, it is appropriate to conclude that questionable teeth should be sacrificed. Dentures can satisfactorily replace extracted teeth.

According to Okell and Elliott,² definite gingival trauma incidental to treatment, or the removal of infected or nonin-

infected teeth, may be followed by a shower of organisms into the blood stream. These observations have been corroborated by Fowler and Tapp in studies conducted in the Abington Memorial Hospital. These findings may account in part for *joint flare-up*, or *temporary exacerbation of pain* which sometimes occurs in various parts of the body after radical treatment of the gums or teeth.

Roentgenograms must be taken from the proper angles and given correct exposure to insure clear definition. The use of *transillumination* and *tests for vitality* may be of some help in making a diagnosis.

The following résumé of 100 cases of arthritis indicates the pathologic condition in the mouth which was removed prior to critical study, and the rather marked amount of *residual infection* in the presence of which it would be difficult to expect complete recovery:

	Atrophic arthritis (53 cases)	Hypertrophic arthritis (36 cases)	Mixed arthritis (11 cases)
Infected teeth extracted before study	21	9	8
Infected teeth revealed by study	25	28	7
Infected roots retained revealed by study . . .	10	2	0
Gingival infection treated before study	0	0	0
Gingival infection revealed by study	44	30	10
Type No. 1	3	1	0
Type No. 2	24	15	2
Type No. 3	16	12	8
Type No. 4	1	2	0

THE NOSE AND THROAT

Infected Tonsils and Adenoids.—The *tonsils* are usually regarded as the most important focus of infection in this region. While it is sometimes difficult to determine, until after removal, whether or not a tonsil is infected, it is usually possible to ascertain this before resorting to operative procedures. Inspection of the anterior pillar for congestion, and withdrawal of the pillar by a retractor, sometimes reveal evidence of underlying infection in the tonsil. Pressure exerted externally to the meridian of the tonsil may yield cheesy masses, liquid, grayish or yellowish pus, or mucopus, as further evidence of the existence of infection. If the infection is deep-seated, it may be necessary to apply a suction cup in order that the contents of the crypts may be expressed and observed. Enlargement of the lymph nodes at the angle of the jaw may be a further important diagnostic point.

Adenoidal tissue in the nasopharynx may be as much a focus of infection as diseased tonsils. Before the removal of this tissue it is not unusual to obtain positive cultures of organisms, and then find that pus is present in the removed tissue.

The retention of diseased tonsils or adenoidal tissue may be the primary activator of focal infection in other organs of the body, viz., the prostate or the intestinal tract. Diseased tonsils should be removed very early in young rheumatoid patients. In elderly persons they may be treated quite successfully and much of their infection reduced by means of local expression of the retained secretion and the local application of antiseptics, such as 2 per cent solution of mercurochrome. Adenoidal tissue may be removed by electrocoagulation.

Many of the so-called "*scratchy throats*" associated with arthritis are often caused by *unrecognized* infected lymphoid tissue. Patients who have had previous tonsillectomies and still have active arthritis should be diligently examined for infection in the regrowths, stumps or tags, and in the small crypts concealed behind the pillars or beneath scar tissue and infected lingual tonsils. The same diligent search should be made for infected lymphoid tissue in the throat.

The following is a brief summary of 100 cases, critically studied, showing the amount of tonsillar infection removed prior to study and the amount of previously undiagnosed additional infection revealed by study:

	Atrophic arthritis (53 cases)	Hypertrophic arthritis (36 cases)	Mixed arthritis (11 cases)
Tonsils removed prior to study	34	6	4
Infected tonsils found upon study	11	21	6
Infected tonsil tags and regrowths found upon study	9	1	0

Sinus Infection.—The nasal accessory sinuses may become acutely or chronically infected and may be a primary cause or activator of arthritis. In many cases, response to therapy for the arthritis is unsatisfactory until local treatment or operative procedures are applied to the sinuses. The ethmoid and maxillary sinuses are the most frequently infected, and pansinusitis may be present. The nose should be thoroughly inspected with a nasal speculum or nasoscope, to determine the state of the membrane and the secretions found. The nasal membranes should be shrunk and the sinuses transilluminated. The patient should be placed in Escats' position for

twenty minutes and the nose again examined for secretions and the location of drainage.

Inspection of the middle turbinate may reveal some infection in the ethmoids, frontals and antra. *Transillumination* is very helpful in the diagnosis of frontal or maxillary disease. The diagnosis of ethmoid and sphenoid sinusitis can best be determined by proper *x-ray examination* of these regions. Where previous infections have thickened the walls of the antra and roentgenograms are questionable, *needle puncture with lavage* may be necessary to complete the diagnostic picture.

Pfahler has found that hyperplastic changes occurring in the membranes of the sinuses which have failed to respond to local treatment will benefit by *x-ray* treatment. A headache may follow these treatments for a period of six to twelve hours, but usually it is not severe enough to interfere with the patient's routine. Following a series of treatments, roentgenograms reveal marked decrease in the hyperplasias of the membranes of the treated sinuses.

Surgical measures are indicated in refractory cases in which polypoid degeneration exists, where infected ethmoids do not respond to treatment, and where frontal and antral membranes are thick and diseased. Surgery is also advised in those cases in which headache and a slight elevation of temperature persist, or a purulent discharge continues, or where the patient's postnasal condition does not improve and the arthritis is still active.

The following tabulation shows the presence of diagnosed sinusitis before critical study, and undiscovered infection revealed by study, in a series of 100 cases.

	Atrophic arthritis (53 cases)	Hypertrophic arthritis (36 cases)	Mixed arthritis (11 cases)
Diagnosis of sinusitis before study	1	1	1
Diagnosis of sinusitis upon critical study	11	7	4

THE GENITO-URINARY TRACT

A careful analysis of the genito-urinary system for possible contributory infection should be considered as a routine procedure. Analyses for infection in the oral cavity and nose and throat are seldom neglected. Unfortunately for the arthritic sufferer, the prostate and seminal vesicles have too infrequently been considered as part of the picture.

Prostatic Infection.—Infections in the prostate are rarely primary among the arthritics studied, and are seldom of

gonococcal origin. There appears to be a relationship with dental and tonsillar infections. In most cases the dental and tonsillar infections are primary and the prostatic infection is secondary. Gastro-intestinal infection may be closely related to infection in the prostate. There is particularly close relationship between spondylitis ossificans ligamentosa and infection in the prostate, in that prostatitis is very frequently associated with this condition.

Examination of the prostate of the arthritic must be thoroughly but cautiously conducted. A digital examination is made of the seminal vesicles and prostate for evidence of gross pathology. A drop of the secretion is examined microscopically on a slide, after first covering the drop with a cover slip. The normal secretion never shows more than five leukocytes to the $\frac{1}{8}$ -inch field, and any number above this should be considered evidence of infection. Clumps of pus cells in the prostatic secretion are evidence of deep-seated infection with poor drainage.

There is a difference between a *focally* infected prostate and one infected as a result of *gonorrhea*. In the prostate infected from previous gonorrhea, all gland follicles become involved and no normal prostatic secretion is present. Pus is everywhere in the field (Pelouze⁶). In prostatic infection secondary to distant foci, the infection may be so deep-seated that it may take two or three consecutive massages of the gland before pus is found in the secretion. If manipulation of the gland causes an increase in joint symptoms even though no pus has been observed on the first, second or third microscopic examination, the gland should be treated, since it is infected and pus will appear later when drainage is established. Even with proper massage, mild reactions usually occur within twelve hours following digital manipulation of the gland. This reaction may last another twelve hours. Usually lesser reactions occur twenty-four to forty-eight hours following prostatic massage. Treatments should not be given more frequently than at three-day intervals. Treatment of the prostate should be properly spaced if other foci are treated; it should not be given on the same day. Prostatic infection cannot be cleared up so long as the causal foci remain.

The following tabulation shows the number of cases of arthritis in which the prostate was found to be infected and contributing to the arthritis before critical study, and the additional infection found in the gland upon further analysis:

	Atrophic arthritis (53 cases)	Hypertrophic arthritis (36 cases)	Mixed arthritis (11 cases)
Infected prostate (before study) in	5 of 17 males	1 of 10 males	0 of 9 males
Prostatitis found (upon critical study) in	7 of 17 males	8 of 10 males	7 of 9 males

Urinary Tract Infection.—In addition to the routine examination of the prostate it is sometimes desirable to examine the urinary tract for infection. Catheterized specimens of urine should be taken for culture where urinary tract infections are considered. Treatment of upper urinary tract infection, such as pyelitis, should depend upon the offending organism. Two previously undiscovered cases of pyelitis were found among fifty-three cases of atrophic arthritis, two among thirty-six cases of hypertrophic arthritis, and one in the group of eleven cases of the mixed type. Urograms are at times used to rule out strictures at the ureteropelvic junction or in the ureters, or to reveal disease in the pelvis of the kidneys, or calculi. A cystoscopic examination is another valuable diagnostic procedure if the urogram fails to reveal the complete picture of the pathology present. Cystitis rarely occurs and when confirmed may respond to medication, or may require bladder lavage. It may occur when fluid intake is low and when constipation is marked, especially in elderly bedridden patients remaining in a fixed position for hours at a time.

Nonspecific Pelvic Infection in Women.—It is quite difficult to establish a direct relationship between arthritis and nonspecific infection in the female pelvis. In many examinations carefully carried out, such foci when found consist of involvement of cervix and endocervical glands with cervical erosions, cysts, salpingitis and parametritis. The cervix might be considered as a point of focal infection because of its lymphatics, some of which pass directly to the parametrium. Others connect with the lymphatics in the body of the uterus, and bear an important relationship to infection of the fallopian tubes and ovaries. When a cervix shows infection, a diligent and careful examination must be made by an experienced gynecologist to determine its extent.

Cervical foci in the nongonorrheal group can be treated by medicaments, douches or actual cautery. By removing the cause of profuse leukorrhea, improvement occurs in the general health of the arthritic. When the cervical glands are chronically involved, conical destruction of the gland-bearing area of the cervix is performed by the electric cautery knife.

The following tabulation shows the number of cases of endocervicitis previously treated, and the undiscovered pathology found upon critical study:

	Atrophic arthritis (53 cases) 36 females	Hypertrophic arthritis (36 cases) 26 females	Mixed arthritis (11 cases) 2 females
Treated previously	2	0	0
Endocervicitis found upon critical study	7	5	0

THE GASTRO-INTESTINAL TRACT

Gallbladder Disease.—Careful investigators have shown that, while the gallbladder should be examined in any complete survey of the arthritic patient and any infection eliminated, it is not a common focus of infection among arthritic subjects. Of greater importance to most arthritics as a site of toxemia is the remainder of the gastro-intestinal tract. Studies at the Abington Memorial Hospital of a group of 100 consecutive active arthritic patients revealed that, in fifty-three patients with atrophic arthritis, *cholecystitis* was present in five rheumatoid arthritics, and *cholelithiasis* in four rheumatoid arthritics. Of thirty-six patients with hypertrophic arthritis, four had *cholecystitis* and five *cholelithiasis*. Of eleven patients with mixed arthritis, three had *cholecystitis* and one *cholelithiasis*.

The above cases were investigated following abnormalities demonstrated by the Graham dye study; some cases showed lack of visualization, poor absorption of the dye and variations of emptying, following the fatty meal. These findings were confirmed by study of the bile recovered by duodenal drainage.

The liver removes toxins and bacteria from the general circulation and acts as a detoxifying organ and bacteriolytic mechanism in infections of the gallbladder. Usually the liver takes care of moderate degrees of gallbladder infection. However, this protective power diminishes with advancing age. Gallbladder disease over a period of years may bring about *secondary changes* in the heart, kidneys, and occasionally in the pancreas, and may be related to arthritis in the joints. An infected gallbladder should be removed because of the pathology involved in the biliary tract and its possible interference with the normal physiologic function.

Cholecystitis should be managed, as in any medical case, by gallbladder drainage, adjustment of diet and medicaments. Surgery should be resorted to on the basis of the pathology in the gallbladder.

The Intestine as a Focus.—The *colon* is frequently mentioned as a focus of infection in chronic arthritis. It is not uncommon to find, after careful study, that a patient may have no foci in the previously discussed locations. Recovery from the disease occurs if careful attention is focused on therapy directed to the intestinal tract. Many arthritics present an intestinal tract in which *visceroptosis* is present. Ptosis is most frequently demonstrable in the colon since it is impossible to get a satisfactory picture of the small intestine. The entire intestinal tract may show an abnormal amount of stasis. The colon may show elongation, dilatation, reduplication, marked tortuosity and at times the presence of diverticula. The stomach may also play its role in the general picture by showing ptosis and hypochlorhydria or achlorhydria. *Toxic products* may originate in such an intestinal tract, especially in the colon, as a result of bacterial activity or improper digestion. These substances may be absorbed in the portal circulation and may play an etiologic role in the arthritis.

Therapy can be directed toward improvement and restoration of normal function. This can best be done through *dietary measures* including an optimal supply of vitamins in which the patient may be deficient. The Vitamin B complex is quite important in this respect since it contributes to the maintenance of normal nerve function in the region of the gastrointestinal tract as well as to the general intestinal tone. These materials tend to produce a more normal anatomic configuration of the colon. A reduction of carbohydrate foodstuffs, with an adequate supply of proteins and fats, is of value in lessening the growth of streptococci in the stools and increasing the absorption of vitamins from the intestinal tract.

Good intestinal drainage is important in the type of case cited above. In addition to diet, other *supplementary measures* may be helpful. The intestinal musculature may share the general muscular asthenia frequently found in arthritics. *Mineral oil*, *agar-agar* and *cascara sagrada* may be used with benefit. *Colonic irrigations* when properly administered are of value. Accumulated toxic products, as well as great numbers of bacteria, are removed by this procedure. When massage of the bowel accompanies the irrigation, improvement in the tone of the bowel accompanies the irrigation, improvement in the tone of the bowel results. Since some absorption of the irrigating fluid may occur during the irrigation, the water entering the portal system dilutes the toxins entering the liver. Bacterial cultures of the stool rarely give information of practical

value. The feces should always be cultured when a history of typhoid fever or intestinal parasitism is elicited.

MULTIPLE FOCI

It may be of interest to note that, in 100 consecutive cases of arthritis picked at random for critical study, many showed more than one focus of infection, as indicated by the following tabulation:

Of 53 atrophic cases:

2	presented	no foci	of infection		
10	"	1 focus	"	"	
14	"	2 foci	"	"	
19	"	3 "	"	"	
6	"	4 "	"	"	

Of 36 hypertrophic cases:

3	presented	1 focus	of infection		
5	"	2 foci	"	"	
15	"	3 "	"	"	
12	"	4 "	"	"	
2	"	5 "	"	"	

Of 11 mixed cases:

2	presented	no foci	of infection		
8	"	3 "	"	"	
1	"	5 "	"	"	

It is evident that if care of foci of infection were limited in these instances to one focus, therapy would be incomplete.

It would seem, therefore, that there is lack of appreciation of the presence of foci of infection and its importance in this syndrome, and that these patients might have failed to respond to therapy if treatment and removal of these infections had been disregarded.

SUMMARY

The evaluation of the role of focal infection in the treatment of arthritis should be considered from the standpoint of the state of the patient's health, as well as upon the basis of the period of time the infection has been present. Hasty diagnostic conclusions and radical removal of suspected foci of infection, without the added careful analysis of all etiologic factors possibly related to such foci, may prevent the patient's recovery and further impair his limited recuperative powers.

The removal of foci even in patients whose arthritis is of many years' duration may be followed not infrequently by

improvement in joints. The early removal of foci may be of great value. In the arthritic clinic of the Abington Memorial Hospital, focal infection is removed only after an "equilibrium" has been established within the major systems of the body.

The presence of foci of infection is harmful to the patient, no matter what his disease. The relationship of focal infection to systemic disease can best be determined after careful analyses have been made by competent consultants in their specialties. Interpretation of their findings should be reached by the internist and not by the "focal specialist" alone. The most careful diagnosis of focal infections and their treatment or removal afford no panacea in the treatment of arthritis, but if the arthritic patient is individualized, such focal infection as may be present will appear in proper perspective in relation to the problem as a whole.

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PHYSICAL THERAPY IN THE TREATMENT OF CHRONIC ARTHRITIS

PHYSICAL therapy refers to the treatment of disease or injury by means of physical agents. It is an *adjunct* to medicine and surgery. The proper application of the physical agents must, of necessity, be known and used by the physician.

In the paragraphs that follow an attempt will be made to describe the physical agents most frequently applied in chronic arthritis, beginning with the simplest. The clinical application and limitations of these procedures will then be mentioned and described. The various clinical types of chronic arthritis will be considered as a group and no differentiation will be made.

In applying a physical procedure to any patient it is desirable to obtain the patient's responses to the type of physical agent used. *Sensory disturbances, circulatory changes* and *scars* should be taken into consideration since any one of these may alter the effect of the treatment. For example, a patient who has lost heat sensation may suffer from overexposure, or one who has a scar may suffer from blister formation, or one who has impaired circulation may suffer from deep ulceration in the application of heat.

Baking.—The method of applying heat by bakers is perhaps the simplest form of applying heat in the treatment of an arthritic joint. Bakers are constructed in various sizes, depending on the part or parts to be treated. The apparatus is an oven-like affair enclosing electric light bulbs of the incandescent type.

The apparatus is placed over the involved joint or joints. The baker should be covered by a blanket to prevent heat loss. The patient's skin should be free of any bandages or ointments. The patient should be made to relax comfortably while undergoing this treatment, which should last for a period of twenty minutes. This treatment may be given daily, or a minimum of

three treatments a week. Following the heat treatment, the joint should be covered and allowed to cool gradually. One must guard against chilling.

In treating *multiple joint involvements*, it is advisable to use a large body baker which covers the patient's entire body with the exception of the head. This type of treatment is more severe and there is profuse sweating, with a consequent loss of body salts and water. To take care of these losses the administration of 15 to 30 grains of sodium chloride followed by two glasses of water is recommended.

Infra-red Irradiation.—This is another form of heat application by means of the infra-red generator. It is best to

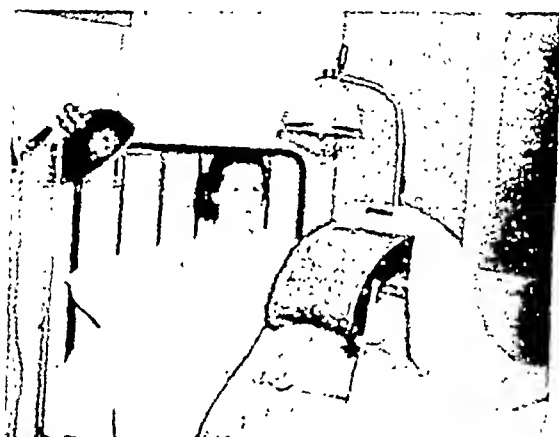


Fig. 197.—Showing application of simple heat methods: Application of baker to knees, Thermo light to right shoulder, infra-red radiation to left shoulder, and complete relaxation of patient.

allow five minutes for the heating of the generator before making application to the skin surface over the affected joint. This form of heat is suitable where *one or two joints are involved*. The distance of the generator from the patient should be such that the patient feels a comfortable heat. This should last for a period of fifteen to twenty minutes.

Luminous Heat Bulbs.—Such bulbs as Thermo lights are used in *localized joint involvements*. The benefit derived is entirely due to the heating characteristics. The tremendous heat thrown out by these lamps makes them more or less dangerous, and they should be used with care and at a *safe distance* from the patient's skin surface. This lamp will heat

the skin surface quickly and tremendously, and in treating an arthritic joint we prefer the slow heat and the prolonged heat. The amount of heat should never reach the stage of discomfort. By increasing the distance of this lamp from the patient a satisfactory treatment will be given.

Diathermy.—Medical diathermy is the production of heat in the body tissues. This modality is applied by three methods:

1. Long wave or conventional diathermy.
2. Short wave diathermy.
3. Induction coil diathermy.

The relative merits of these procedures are still in the controversial stage and will not be discussed here. It is suf-

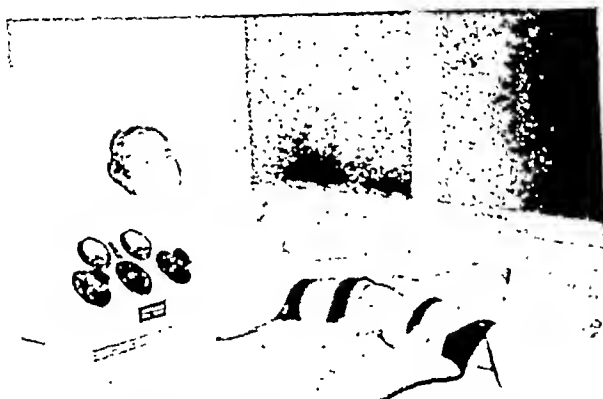


Fig. 198.—Treating a chronic arthritic knee joint by short wave radiation: rubber electrodes above and below knee joint, knee slightly flexed. Perfect relaxation of patient.

ficient to say that all three methods will induce heat in the deep tissues, including the joint structures.

The *long wave*, or *conventional*, diathermy produces slower temperature rise locally over a longer period of time. The metal electrodes come in direct contact with the skin surface. Care must be taken in the application of the metal electrodes. K-Y jelly or soap may be used to insure good skin contact; otherwise sparking occurs with resultant burns. One or two joints may be treated simultaneously by means of bifurcated cords. Equal-sized electrodes may be used above and below the joint in the form of cuffs. The duration of treatments is varied from thirty to forty-five minutes.

Short wave diathermy is more direct in its action. The body acting as a condenser, the electrodes are spaced about $\frac{1}{2}$ inch from the skin surface. Rubber-covered electrodes are used, with felt or towels $\frac{1}{2}$ inch thick next to the skin. In place of the latter, glass air-spaced electrodes may be used in contact with the skin surface.

The electrodes are placed either above or below the joints anterior or posterior, or laterally to the joints. The duration of the treatment is dependent on the power of the apparatus and ranges from ten to twenty minutes. *Do not treat through the clothes.*

Induction Coil Method.—The current is conducted to the patient by means of a very flexible cable which is insulated. The cable is coiled about or wrapped around the joint to be treated. The duration of the treatment varies from twenty to thirty minutes.

In giving any one of these diathermy treatments it is necessary to be careful that *no metal comes in contact with the patient or the machinery*. Metal chairs, metal beds, or spring mattresses should not be used, for shocking and severe burns may result. There is also a tendency for the metal furniture to draw the current away from the parts or part which is under treatment, thereby making the treatment ineffective.

Diathermy treatments are given on an average of *at least three times weekly*, although there are no contraindications to daily treatments. One or two treatments weekly produce little or no results.

Hyperpyrexia.—Hyperpyrexia induced by physical agents is a long-drawn-out procedure which is time-consuming, expensive, and which subjects the patient to considerable mental and physical exhaustion. Among the arthritics, particular care must be exercised, especially in the *selection of cases* as to risks. The cardiorenal mechanism must be in excellent condition. Reports show that the results are good in only a few selected cases, usually among the early acute cases associated with gonococcal infection.

Paraffin Baths.—Another means of applying heat is with the paraffin bath. The paraffin is melted in a double boiler, care being taken that a piece is left unmelted or, otherwise, burns may result.

If the joints of *fingers, hand or wrist* are affected, the hand is dipped into the paraffin, keeping the fingers separated. Do not touch side or bottom of boiler. Remove the hands from the boiler and the paraffin is allowed to harden. Again dip and

quickly remove. Repeat this process until a thick glove is formed. Allow the paraffin to remain on for one half to one hour; then peel off and put paraffin back into the boiler.

If paraffin is applied to *knee joint*, *elbow joint*, *spine* or *ankle joint*, a new paint brush is used to apply the paraffin to the affected part. Apply it until you get a thickness of $\frac{1}{8}$ inch and allow it to remain on for from one-half to one hour.

The above procedures may be done at least three times weekly; or, if the procedure is carried on at home, it may be done three times daily. The value of the paraffin bath is attributed to the fact that heat is effectively retained for considerable periods.

Mud Baths and Mud Packs.—These are recommended for general and local use in chronic arthritis, especially in the presence of capsular swelling. The essential effect is that of heat; the mud has high heat retention and low heat conductivity, higher temperatures can, therefore, be maintained.

Massage.—Massage is the manipulation of the soft tissues of the body. It is important that such massage of an arthritic be gentle and purposeful. The heat treatment usually precedes the massage, for the heat prepares the tissues by giving them proper relaxation and a better blood supply.

In a massage, the joint should be completely relaxed and comfortable, clothing and restricting bands being removed. In giving the massage the hand or hands should mold the surface of the tissues and should move smoothly. If necessary, cocoa butter, cold cream or olive oil may be used; or, if the skin is moist or sticky, alcohol or talcum powder can be used. The massage should not cause pain and the hands should be kept in contact with the skin surface at all times. Do not pinch the tissues. A stroking movement should be used. The depth of the stroke depends on the toughness and resistance of the tissues. The heavier stroking should be upward, the lighter stroke downward. Pemberton advocates that massage of an arthritic joint be confined to the regions *below* and *above* the joint, for it is at these places that circulation can really be increased. Five minutes of massage to a joint is sufficient; a longer massage often tends to traumatize the already weakened tissues.

Pemberton, in his recent book on arthritis, gives *four indications* for the use of massage in arthritis:

1. To prevent or delay muscle atrophy and to restore tissue when atrophy has taken place.
2. To improve local and general metabolism.

3. To increase circulation of the local tissues.
4. To promote muscle contraction of the limb, thereby stimulating venous blood flow.

Pemberton also mentions the value of massage to overcome the *edema of the dependent parts* in chronic arthritis, especially when patients are confined to bed or chair. General body massage is often indicated, especially in those arthritics who have been chair- or bedfast. This procedure may, in the conditioned subject, be extended to an hour. Care must be exercised at all times so as not to fatigue the patient.

Ultraviolet Irradiation.—Ultraviolet irradiations are *contraindicated* in febrile conditions. This limitation is often overlooked. The arthritic patient is frequently in need of ultraviolet and oftentimes shows remarkable results. The local reaction of the skin to the ultraviolet rays is an erythema; this develops in a period of from one to five hours and usually disappears within twenty-four hours. The erythema is associated with an enlargement of the capillary vessels. This vasodilatory reaction is not confined to the irradiated surface but extends deeply into the tissues. Blood regeneration in anemic conditions is often stimulated by this procedure. The erythema-producing rays, in normal doses, evoke a rise in the bactericidal elements of the blood. It cannot be said that the important subject of the full mechanism of the blood reactions is yet satisfactorily understood.

The *general systemic effects* of the ultraviolet rays on the body which are beneficial to the arthritic include an altered metabolism which is shown in the improved appetite and sleep, increased assimilation and diuresis, mental stimulation through action on the central nervous system, improvement of skin tone, and the formation of vitamins and provitamins. Ultraviolet rays may be obtained from various sources, direct sunlight and ultraviolet lamps of various types.

In *preparing the patient* for irradiation treatment, either natural or artificial, it is necessary that the skin surface be free from any grease, ointments, powders or other medications and that the skin be exposed directly. In giving sunlight treatments, the patient's eyes should be protected, either by dark glasses or moistened cotton sponges. If natural sunlight is utilized, the best time for exposure is about 11 A.M. The nurse or the patient should be advised of the importance of this consideration. The first exposure should not exceed fifteen minutes, which time is increased by fifteen minutes with each

subsequent exposure. The patient may be exposed anteriorly and posteriorly the same day or on alternate days. Care must be taken not to overexpose the patient. Some serious complications have resulted as a result of neglect of this precaution.

Ultraviolet Lamps.—These are utilized when the patients are unable to be taken out into the direct sunlight, either because of bad weather conditions or because of lack of proper facilities to move the patient. The patient should be prepared by cleansing the skin surface and protecting his eyes. Treatment under a lamp should begin with two minutes at a distance of 36 inches, but the dosage may vary depending on the strength of the lamp and the patient's tolerance. The patient may be treated by one exposure anteriorly, and increasing the duration of the treatment one minute with each application and keeping it at five minutes. The patient may be treated by first exposing the upper half anteriorly, then the lower half, and doing the same thing posteriorly, using the same dosage. These treatments may be given daily or three times a week. Occasionally an arthritic will show good response by just exposing the affected joints to the ultraviolet rays.

Galvanic Current.—When considering galvanic currents it is always necessary to consider the effects of polarity. The galvanic current is a direct current possessing actively positive and negative poles.

In the treatment of an arthritic joint, the galvanic current may be used. A painful joint may be given relief from pain by application of the *positive* pole, because this has a tendency to reduce nerve irritability and to produce vasoconstriction. On the other hand, relief of joint pain may be secured by the application of the *negative* pole, which acts as a counterirritant by increasing nerve irritability and produces vasodilatation. The effects are purely the result of this reaction.

Iontophoresis.—Iontophoresis is employed for the introduction of drugs with local vasodilating effect by means of the galvanic current. The drugs that are most commonly used at present are *histamine* and *mecholy* in 1 per cent aqueous solutions or in ointment form.

Both of these drugs, when introduced into the tissues through the skin's surface, produce marked vasodilatation at the site of application. This vasodilatation is maintained for a period of from twelve to twenty-four hours. The action is partly one of counterirritation. However, if treatment is prolonged, there will be considerable absorption of the drugs with

resultant systemic effects. These drugs should not be used on those patients who are prone to asthmatic attacks or who have cardiac involvement.

Technic.—If the aqueous solution of histamine or mecholyl is used, a piece of asbestos paper or paper toweling is saturated with the desired solution. This asbestos paper or paper toweling is then wrapped about the joint to be treated. The positive metal electrode is then applied on top of this. The negative electrode is applied elsewhere on the body. This should be large and dispersive. The current is then turned on to the point of tolerance, usually requiring about 20 milliamperes. Duration is ten to twenty minutes. At the end of the treatment the current is reduced slowly and is then turned off. On removing the electrodes and the paper toweling or the asbestos paper, the skin will show marked redness with urticarial blotches. If the ointment is used instead of the aqueous solution, the ointment is rubbed over the affected region. The asbestos paper or paper toweling is saturated with water and the positive metal electrode placed over this and we proceed in the same manner.

In giving any of the above treatments with galvanic current, be sure that there is *sufficient thickness* of asbestos paper or paper toweling so that, when the metal electrode is applied, there is no possibility of it contacting directly with the skin; otherwise, a resultant deep galvanic burn will take place.

Hydrotherapy.—Chronic arthritis or rheumatism is not a disease of certain joints but a constitutional disorder in which the circulatory, metabolic and gastro-intestinal systems are involved. It may take the form of a neuritis, myositis, fasciitis, fibrositis or arthritis, depending on the tissues involved. Hydrotherapy is valuable in that it produces increased circulation and metabolism.

The *full tub bath*, given at a water temperature of 100° F. for a period of twenty minutes, is sometimes indicated in polyarthritis. While the patient is in the water, he should try active movements of all the joints. These patients should be carefully watched and, occasionally, should be assisted in their movements. The room temperature should be 75° or 80° F. to prevent the patient from getting cold.

For those arthritics who are unable to take a full tub bath, Coulter describes the application of the *full wet pack*; this consists of wrapping the patient in a warm moist sheet with dry blankets over this and allowing him to remain for forty-five minutes. Body bakers, Thermo lights, infra-red irradiations, or

hot water bags may be used in conjunction with this application to help keep the subject at the desired temperature. These systemic treatments are given at least twice weekly and not more than three times weekly.

Hydrogymnastics are sometimes desirable and are conducted by immersing the patient in a heated pool at a temperature of 102° F. and allowing him to exercise the painful joints under water. The bath may last thirty minutes, but it should not be given to the weak or debilitated arthritics. The *Hubbard* tank, improved by Currence, has been devised for hospital use. This enables the arthritic not only to receive the movements necessary under water, but the whirling motion of the water also gives him a gentle massage.

Whirlpool baths are given either to the upper or the lower extremities at a temperature of 110° F. for twenty minutes. The whirling produced by water under air pressure gives an efficient and gentle massage to the painful joint. Joint motion which otherwise could not be tolerated because of pain may be given while in the whirlpool bath.

Sodium or *carbon dioxide baths* owe their effects purely to the generalized peripheral vasodilatation and counterirritation. These baths at present can be produced artificially, with the same results as with natural water. The warm, magnesium-sulfate full-tub bath given at a temperature of 100° F. for thirty minutes is a useful household treatment, using proportions of 1 pound of Epsom salts to a tubful of water; this is often sufficient to afford relief from painful joints. These baths should be given at least twice and not over three times weekly. The procedure is *contraindicated* in the case of weak and debilitated patients.

The local application of *hot magnesium-sulfate packs* is favored by a good many. In applying such packs the temperature should be 103° F. and the packs should be at least 1 inch thick. The solution should consist of 2 teaspoons of magnesium sulfate to 1 quart of water. The joint should be completely wrapped in the pack and the pack should remain on for at least an hour; this should be repeated every three to four hours. Again a baker or Thermo light may be used to maintain heat.

Colonic Irrigations.—These are of considerable value in selected cases of chronic arthritis. In such cases a series of colonic irrigations is followed by a marked improvement in symptoms. Ordinary tap water is used at a temperature of 100° F. One hour before beginning the irrigation the patient

should always have an *enema*, otherwise the irrigation will prove a failure.

With the patient lying on his left side with the right knee flexed to 90 degrees, 8 ounces of water is introduced into the rectum and the abdomen is gently massaged. The water is expelled, and the process is repeated until 2 or 3 gallons of water have been utilized. The patient *should never* experience any sensation of pain or distention. The irrigations are repeated twice weekly and should be given in a series of six, with a rest period of two weeks.

Barring all contraindications to the irrigation, *abdominal massage* is given at the same time. Pemberton's "8 Point" colonic massage is most efficient. This consists in beginning

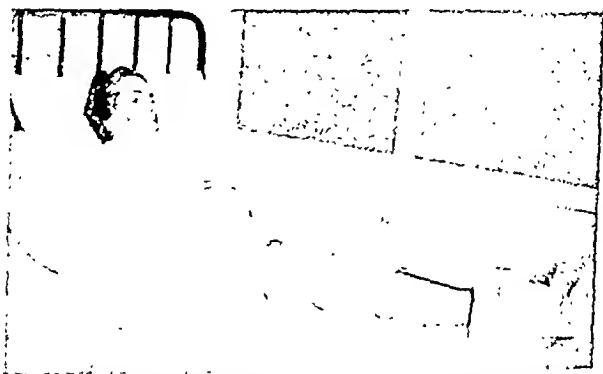


Fig. 199.—Application of a hot pack to knee: Note pack comes well above and below knee. Pack at least 1 inch thick. Note complete relaxation of patient.

the massage at the lower left quadrant and progressing distally toward the rectum, after which another point is selected 2 or 3 inches higher and the same processes repeated, until final massage begins at head of colon and progresses the entire length to the descending sigmoid.

Exercise.—The value of exercise for the maintenance of health is generally known, the resulting increase in circulation benefiting all parts of the body. In the arthritic, exercise *must* be *limited* and *selected*.

Passive exercise, limited in extent, is necessary to prevent adhesions and contractions of the joints. The movements should be gentle and without pain. *Never force a joint*, for this is very apt to produce a flare-up in the condition.

Active exercise may be employed to restore muscle function. All structures producing motion must be considered part of the joint: the ligaments, muscles, synovial membranes, the nerves and the blood vessels. The active exercise should be limited to the point where the patient begins to feel pain and fatigue. If the patient is too weak, the active movements may be assisted. When the joints are stiff and will not function freely, the patient should be encouraged to move the muscles about the joint actively, *i. e.*, so-called muscle setting. In the presence of pain or inflammation, motion about the joint is contraindicated.

Occupational Therapy.—This form of treatment should be devised to meet individual requirements and should include



Fig. 200.—Colonic irrigation. The patient lies on his left side with right leg flexed. Marking on irrigator: each line indicates 8 ounces. Thermometer in irrigator denotes temperature of water.

not only *physical*, but also *mental* occupation. Occupational therapy is applicable chiefly to the convalescent and has a very limited place in the regimen for patients who are acutely ill or for whom complete rest is essential.

Posture.—Permitting the chronic arthritic to become deformed is poor treatment. Poor posture is a potential factor in arthritis, and early steps should be taken toward *prevention* rather than correction. The purpose is to get these muscles in balance so that proper tone will develop. The physician should be the one to demonstrate and give proper postural exercise as indicated to meet the requirements of the patient.

Rest.—Fatigue is almost always present in chronic arthri-

tis and, therefore, general rest, both *physical* and *mental*, is essential. Rest in bed should be in a position of good posture. The bed should not sag; the spine is to be kept straight allowing only one pillow under the head. No pillows are to be allowed under the knees. The patient should not be kept in one position for too long a period, frequent changes of position being indicated to prevent pressure sores and stiffness. Mental rest and relaxation is secured by eliminating various mental annoyances, such as visitors and household details.

Local Rest.—The affected joint should be kept at rest. This procedure should be prescribed judiciously and the position of rest should be the position of maximum function. Molded plaster splints are best utilized for joint rest. Later, braces may prove necessary as a supportive measure. *Do not immobilize the joint over too long a period*, for this may eventually lead to joint stiffness. Passive motion and massage should be instituted at the earliest possible moment during the course of a splinting procedure.

CLINIC OF DR. CHARLES WILLIAM DUNN

ABINGTON MEMORIAL HOSPITAL

PRESENT STATUS OF ENDOCRINE THERAPY IN ARTHRITIS

Arthritis and the Menopause.—Arthritic pains and pathology are often observed in endocrine disorders. Arthritic manifestations without osseous pathology, termed "*menopausal arthralgia*," may occur as part of the menopause. Holmes believes that the diagnosis "menopause arthritis" should be limited to arthritis commencing within five to six years preceding or following cessation of menstruation. The onset is usually insidious and is accompanied by a tendency to gain weight. A sudden exacerbation of pain in the knees is experienced, with the appearance of painful swelling of one or more of the terminal finger joints. In his opinion, the joint signs are exactly those of other forms of chronic synovitis in the early stages. x-Rays reveal no bony changes in the early stages, but later bony spicules appear and, still later,ipping and loose bodies develop.

Zondek writes, "The climacteric affects the entire body. During the climacteric there is found, especially in women, a tendency to chronic affection of the joints."

Maranon found that the incidence of arthritis varied with the *type of obesity* occurring at the menopause. In Type 1 the woman has always been robust and during the climacterium a rapid weight gain of the plethoric type occurs. Type 2 has always been of an asthenic constitution and, during the climacterium, gradually gains weight. In Type 2 the incidence of arthritis is less frequent, as is also osteoporosis and a slight increase of blood calcium. Type 1 also shows a diminished carbohydrate metabolism, occasional glycosuria, hypertension and hypertrichosis. Maranon believes that Type 1 results from overactivity of the hypophysis and suprarenals and underaction of the thyroid. Type 2 from underactivity of the hypophysis and suprarenals and overaction of the thyroid. Whether or

not all will agree with Maranon's endocrine interpretation of the two types of climacteric obese patients with arthritis, this differential analysis of the disturbed endocrine interrelationship, with both types having a hypoovarian syndrome, is worth noting.

Arthritis and Pregnancy.—The spontaneous cures, remissions or improvements reported by Hench show that arthritic patients who have experienced relief from their arthritis during pregnancy have intentionally become pregnant to obtain relief again.

Two *hormones*, namely the *estrogens* and *A. P. L.* substances, are present in excessive amounts during the pregnant state. Arthritic patients state that during their pregnancy relief does not occur until from one to three months, and as late as five months, after conception. Apparently it is not until the estrogenic and/or the anterior pituitary-like substance concentration in the blood reaches the abnormally high levels of the first to third months of pregnancy (which levels persist until after delivery) that the arthritic condition is benefited. After delivery the persistence of relief from the arthritic state varies widely. The arthritis may recur a short time after delivery, or not for a period of many months. After delivery of the placenta, the abnormally high estrogenic and anterior pituitary-like content of the blood and urine terminates, since the placenta is the source, during pregnancy, of these hormones.

Thus from an indirect biological approach, we can correlate the relief from arthritis during pregnancy (most probably) with the *high estrogenic blood content* of pregnancy. The amount of relief experienced by the arthritic patient during pregnancy may, however, be complete, variable, or even absent. The estrogen content of the blood and urine in pregnancies, while always high above normal, *varies widely* in individual pregnancies. Accordingly, a failure to obtain relief of the arthritis in all pregnancies does not invalidate its role. Pregnancy is also known to affect favorably chronic sufferers from *migraine*; in fact, the variability of its effectiveness is that which is similarly observed in arthritis.

Our experience suggests that patients with arthritis who do not experience relief during pregnancy should receive estrogenic therapy.

The Role of Estrogenic Substance in Arthritis.—Evidence for the role of estrogenic substance in arthritis is obtained by a study of arthritis during the menopause. The

onset of arthritis here occurs at or about the time of the menopause, or an existing arthritis is aggravated by the reduction or cessation of ovarian function. Arthritis, therefore, is presumptively associated, in a definite group of cases, with low or absent ovarian function and the resultant subnormal or absent estrogenic blood values. One of the observable phenomena frequently associated with menstruation (particularly abnormal menses) is the tendency of the body, during the premenstrual period, to retain fluids and show a gain in weight. Menopausal patients complain of generalized fluid retention as well as a localized swelling in the joints. The clinical description which the menopausal and hypomenorrheal arthritic cases give is that of swelling, stiffness, tenseness and pain in the joints before, during and following the menses. In individuals having the menopausal type of amenorrhea the periods of pain are worse at the time of the month the period should normally occur. One is tempted to suggest that a part of the pathology producing the arthritic pain in the estrogenic deficiency case is the abnormal increase in fluid content of the joint tissues.

The reports on estrogenic therapy in arthritis by Cohen, Dubbs and Myers and by Greene and Ryan show that little benefit is obtained from estrogenic therapy in arthritic females in whom no menstrual disturbance exists. Cawadias states that the indications of estrogenic therapy are based on a precise differential diagnosis between the various hypoovarian conditions.

Two British reports published in 1933 advanced the importance of endocrine disorders in arthritis occurring in the female sex. One revealed a 23.7 per cent incidence of arthritis and fibrositis in 1000 women at the menopausal age; the other a definite incidence of thyroid deficiency in cases of arthritis. In 1936 Hall reported the effect of estrogenic substance in menopausal arthritis. A group of forty-nine women with a natural or artificial menopause who had symptoms of the menopause and arthritis were treated with estrogens (*Progyon*, *Theclin*). Estrogenic therapy was effective in 91 per cent of twenty-two with arthralgia alone, 66 per cent of the eighteen with atrophic arthritis and 44 per cent of the nine patients with hypertrophic arthritis. Hall subsequently reported a series of seventy-one women whose arthritis developed after castration. Of these, fifty-three suffered from "arthralgia rather than true arthritis." Of forty adequately treated with estrogenic substance, 80 per cent experienced from 50 to 100 per cent relief and 70 per cent responded to the

extent of almost complete relief from the menopausal symptoms and the arthralgia. There were eighteen cases of atrophic or hypertrophic arthritis (or mixed), and 50 per cent of those with menopause symptoms and arthralgia were relieved of their symptoms. In some of the remaining cases the arthritic state was apparently improved by estrogenic therapy. Estrogenic therapy proved equally effective in 50 per cent of the cases of true arthritis.

Dosage and Duration of Estrogen Therapy in Menopausal Arthritis.—In arthritic cases treated with estrogenic substance, the dosage and duration of estrogenic therapy and the method of administration are very important. Hall states, "Our failure in the past has been largely due to inadequate therapy. . . . An important part of the rationale is the introduction of a substance which inhibits overactivity of the anterior pituitary gland." The dose of estrogenic substance administered to these patients varied considerably. Generally 2,000 R. U. twice a week was administered, but in some cases five times as much was required. Effective relief of symptoms did not appear until estrogenic therapy had been administered for from three to six weeks. The menopausal symptoms were relieved early, in order of their onset, and lastly the arthritis was relieved. Most of the patients were treated with large doses of estrogenic substance over many weeks, some for months and years. Hall believes too much estrogenic therapy may be given. The appearance of a sore or swollen breast, the sense of pelvic congestion, leukorrhea and general malaise indicate that less or no therapy is needed. Hall is of the opinion that but a single step separates the clinical pattern of menopausal arthralgia from the true arthritis which occurred in castrates who had been well until castration occurred.

Atrophic Arthritis.—Cohen, Dubbs and Myers noted that in the majority of their cases of atrophic arthritis treated with estrogenic substance the improvement was of a general nature. Joint conditions per se, if secondary to hypertrophic changes, remained the same unless posture and weight were corrected. Their twenty-three cases of arthritis (seventeen atrophic, six mixed but atrophic and hypertrophic) were treated with *Progyon B*. Twelve patients experienced distinct improvement in joint symptoms while under therapy, three noted some improvement and then relapsed, seven noted no improvement, and one said she was worse. Of eighteen patients, all but six of whom still had active menopausal symptoms, seven noted improvement in joint symptoms as well as in the subjective phe-

nomena related to the menopause while four noted a general improvement with no effect on the joint symptoms.

The *duration* of treatment varied from one week to three months, and the total *dosage* varied from 10,000 R. U. to 170,000 R. U. Individual doses ranged from 2,000 R. U. to 20,000 R. U. In the beginning the patients were given an intermenstrual injection of 2,000 R. U. daily and, when improvement was noted, the interval was reduced to once a week. If no improvement was noted, the dose was gradually increased to 20,000 R. U. After three or four such doses, if no change was noted, treatment was discontinued. Twelve sufferers from atrophic arthritis, moderately advanced, without menstrual disturbances, were used as controls. Each was given 10,000 R. U. of estrogenic substance daily for from one to three weeks. None showed any response. They concluded that the joint symptoms *per se* must be treated by clinical readjustment. Atrophic arthritis occurring concomitantly with the menopause was benefited in a sufficient percentage of cases to suggest that this form of therapy has a definite place in the treatment of such cases of atrophic arthritis.

The number of patients in this series in whom menopausal symptoms persisted during therapy and the early abandonment of therapy, in contrast to the longer duration of therapy advised by Hall and others, suggest that inadequate therapy might be responsible for some of the failures herein reported.

Other Cases of Arthritis in Which Estrogenic Substance Was Used.—Greene and Ryan report that of their thirteen arthritic cases with menstrual abnormalities only four completely failed to improve. Woodhead used Progynon B with success in two *males* suffering from arthritis. The results were dramatic. From the second injection pain was reduced and swelling and stiffness disappeared rapidly. The second case was a severe one of atrophic arthritis: a man who could not put on his coat alone. He was given 25,000 International benzoate units of Progynon B twice a week. At the end of the first week he could put his coat on alone and was beginning to walk better. Woodhead warns of the danger of causing enlargement of the prostate gland and suggests the administration of testosterone at the end of the treatment.

The use of estrogenic substance in the male is not totally unphysiologic or unbiologic because the male normally possesses an estimable titre of estrogenic substance. The author has used estrogenic substance effectively in males with migraine. The first abnormal reaction appears to be in the breast

tissue. Estrogenic gynecomastia appears to occur before prostatic tissue is affected. In five cases in which temporary gynecomastia was induced in males no prostatic symptoms occurred.

Bauer has failed to observe effective results in a limited number of arthritic cases treated with estrogenic substance. In the author's experience it has been necessary in arthritic cases with severe menopausal symptoms to give even larger doses than those administered by Bauer to obtain results, both on the menopausal symptoms and on the arthritis. Usually more satisfactory results are obtained with larger single doses, *e. g.*, 20,000 to 30,000 R. U. every third day for nine days, than with the administration of 10,000 R. U. of Progyon B every day for nine days. In fact, in our experience, symptoms have occasionally been aggravated by low dosage and effectively controlled by markedly increasing the dosage of estrogen administered.

The case of M. C., a woman, first examined in July, 1937 at the age of thirty-nine years, well illustrates the problem and principles of endocrine therapy in arthritis:

Summarizing the two and one-third years of therapy, we observe that thyroid therapy, while effecting an elevation of the basal metabolic rate from minus 26 to minus 2, produced no improvement in the patient's arthritic state and a progressive menopausal syndrome developed. Ovarian extract was ineffective because of its inertness. Oral administration of emmenin was effective in relieving, first, her menopausal symptoms and, subsequently, the arthritic state, but was ineffective for the recurrence of the symptoms; whereas Progyon B (estradiol benzoate), 2,000 R. U. weekly by hypodermic, relieved both the menopausal syndrome and the arthritic pain. The effectiveness of hypodermic over oral administration of estrogenic substances for the recurrence of the symptoms is explained by the fact that the patient was now one year older, her menopausal state was more advanced, and her estrogenic deficiency state was more pronounced.

In November, 1939, the patient again had a recurrence of hot flashes, depression and arthritic pains in the knees, fingers and toes. The synthetic estrogenic substance, Stilbestrol, 1 mg. every other night, was administered. At the end of three weeks there was a loss of weight of 3 pounds, the arthritic pains were considerably less, hot flashes were inconsequential, and the periods of depression were negligible. The patient is now taking Stilbestrol, 1 mg. every third day, with excellent control of her menopausal state and arthritis. Whereas the patient responded to the administration of the natural and synthetic estrogenic substance, the administration of an inert endocrine preparation, ovarian extract, was inadequate.

This case illustrates the fact that both *orally* and *hypodermically* administered estrogenic substances are effective in arthritis. When oral administration fails to relieve symptoms, this does not necessarily create a negative result for endocrine

therapy, because hypodermic administration of estrogenic substance is required for the more advanced menopausal age, with or without arthritis. It further indicates that Stilbestrol, a synthetic chemical substance possessing estrogenic properties, is fully as effective as the naturally occurring hormone in arthritis. This last observation brings to the forefront the *chemical factor* in the problem of arthritis therapy. Hench called attention to the fact that sex hormone, Vitamin D, and the bile salts are chemically related. All have in one manner or another shown evidence of producing a remedial effect on arthritis.

It is extremely unlikely that endocrine therapy can materially affect or revert to normalcy gross arthritic pathology, with the possible exception of fluid deposition in the cellular tissue composing the articular structures. Accordingly, the general principles of arthritic therapy must be carried out *in conjunction with* the use of endocrine products.

In the menopausal patient, not *every* pain occurring in the region of an articulation is an arthritic pain, even though arthritic changes may be present in another region. For example, a patient (M. C.) began to have pain in the articular areas of the posterior cervical region and the suboccipital area, which appeared during a progression of the menopausal symptoms and with an aggravation of her previously existing joint symptoms. This posterior cervical and suboccipital pain, which is commonly associated with tenderness and some limitations of neck motion, is, in the author's opinion, neither arthritis nor arthralgia because it is a common symptom of the menopause and is too consistently relieved by one or two injections of from 2,000 R. U. to 6,000 R. U. of Progynon B, an impossible feat in true arthritis or arthralgia. Furthermore, x-rays of the cervical vertebrae are always negative in the menopausal, nonarthritic case.

When estrogenic therapy is administered to patients with menopausal arthritis, one observes that before the arthritic pains are measurably influenced the hot flashes, sweating, palpitations, nervous irritability, head pressure pains and mental changes are affected before the joint symptoms show improvement. In other words, the *existing estrogenic deficiency state* must be corrected and the basic hypoovarian symptoms relieved *before* one can affect the later occurring arthritis in the menopausal syndrome. Similar observations of the effect of estrogenic therapy in arthritis have been made by Hall, Kurzrok and others.

Arthritis and Hypothyroidism.—Hypothyroidism, more particularly the severer form of thyroid deficiency, *myxedema*, frequently has an etiologic role in arthritis. It appears that only in the more *advanced forms* of thyroid deficiency is the incidence of arthritis significant.

Hartsock found that there is a *seasonal variation* in the amount of thyroid extract required, a larger amount being required in cold weather. This seasonal variation of thyroid extract requirement is of extreme importance and far too few writers refer to it. Hartsock further recommends that thyroid extract be administered *early in the day*, even when the basal metabolic rate is well below normal.

Hall and Monroe studied 300 patients with chronic, non-tuberculous arthritis with reference to their basal metabolic rates, action of thyroid gland therapy and results of medical treatment which included thyroid substance. Of these, 150 were of the atrophic type of arthritis and 150 of the hypertrophic type. Thyroid gland therapy was of permanent beneficial effect in 49.1 per cent of 115 hypertrophic cases in which it seemed wise to use it. In the atrophic group, definite glandular deficiency seemed present in only a small number and there was usually another explanation for the hypometabolism.

Rawls *et al.* found that only 20 per cent of the patients with markedly active rheumatoid arthritis showed improvement when administered thyroid extract, with many patients tolerating only small doses; it was, in fact, sometimes necessary to discontinue therapy. Forty-one per cent of the patients with mixed and osteoarthritis improved following the administration of thyroid extract. Osteoarthritis of the hip, spine or shoulders did not respond to the administration of thyroid extract. Obese women exhibited swelling of the arthritic joints and often showed excellent results from treatment with thyroid extract. Rawls was able less frequently to elevate the basal metabolic rate and effect improvement by the administration of thyroid extract in the rheumatoid arthritic group.

Indications for Thyroid Therapy in Arthritis.—In our experience, we have found that thyroid extract is most effective in the treatment of arthritis when other signs of hypothyroidism can be determined. The *hypothyroid symptoms* are in many instances the so-called "minor" or "atypical" evidences of hypothyroidism: intolerance to cold weather, sensation of chilliness in a room which is comfortable to others, persistent subnormal temperature, tendency to recurrence of acute and subacute catarrhal conditions chiefly of the respiratory system

and lowered resistance, minor gastro-intestinal disturbances, anorexia, indigestion, flatulence, sluggish elimination (renal and intestinal), constipation, varying degrees of mental and physical lassitude, fluid retention, dryness and thinning of the scalp and body hair, thinning of the outer third of the eyebrows, diminished perspiration, dryness of the skin, and *tache pulvérisée* (by this the author means that by stroking the fingernail on the skin in the direction of the venous flow a powdered line occurs over the region stroked; this has been found to be a most valuable physical sign of the presence and degree of hypothyroidism).

It should further be noted that even in cases of severe hypothyroidism, as myxedema, only one major sign of hypothyroidism may exist, such as secondary anemia; achlorhydria; infiltration of the skin, generalized or localized; and, in the latter state, the patient may as a matter of fact appear to be nephritic.

It is a false premise to establish a diagnosis of hypothyroidism on the basis of a *low basal metabolic rate alone*, even when of minus 30 or minus 40. It should be kept in mind that anterior pituitary deficiency and hypoovarian cases, particularly the former, occasionally have basal metabolic rates within this low range. In such cases the *tache pulvérisée* is absent. Thyroid extract will not elevate the basal metabolic rate to normal in these cases without the development of thyrotoxic symptoms. In evaluating the diagnostic importance of a basal metabolic rate one should always remember that the range of normal is wide—from 20 to 30 points. A primary anterior pituitary deficiency has a secondary hypothyroid phase, but usually only a small amount of thyroid extract is required to control this. Anterior pituitary substance, orally or by hypodermic, is the main therapeutic agent required. In our experience it is the anterior pituitary deficiency case with a low basal metabolic rate which quickly develops intolerance to thyroid therapy, for reasons indicated. The basal metabolic rate is, nevertheless, a reliable indicator of both the probably required dosage of thyroid extract and sufficiency of therapy in true hypothyroidism.

Another measurable indicator is the *temperature-elevating effect of thyroid extract* on the *subnormal temperature* often present in hypothyroidism. A combination of thyroid extract and estrogenic substance is sometimes advocated in arthritis of the menopausal age. The type of menopausal arthritis case which is most favorably and promptly affected by thyroid

extract is one in which swelling in or about the articular tissues is present.

The *menopausal syndrome* frequently appears as a *pseudo-hyperthyroid state*, the complaints being a sense of fulness in the thyroid region, nervousness, activation, vasomotor disturbances, palpitation and insomnia. In the initial clinical appraisal of the case, therefore, thyroid extract appears to be contraindicated. The administration of estrogenic substance, however, promptly controls the pseudo-hyperthyroid state, and not until then is the true state apparent and the need for thyroid extract evident. In the main, this type of case tolerates only low dosage of thyroid extract— $\frac{1}{4}$ grain to $\frac{1}{2}$ grain daily—and toleration is usually optimal when thyroid extract is administered in the morning.

The most that can be said for thyroid therapy in arthritis is that it acts best when a frank thyroid deficiency, such as myxedema, coexists. In the milder hypothyroid states its favorable effect on the arthritis becomes less evident. Its general metabolic effect, however, and particularly its effect on improving elimination with the resultant increased physical and mental drive, enhances its value as a therapeutic agent in the general arthritic regimen in a definite group of cases.

Dosage of Thyroid Extract.—The dosage of thyroid extract quite naturally varies with the degree of the thyroid deficiency present. Generally, it is preferable to begin thyroid therapy with a dosage smaller than the estimated requirement, *e. g.*, $\frac{1}{4}$ to $\frac{1}{2}$ grain daily, and, at weekly intervals, gradually increase the dosage to the physiologic level desired. This procedure is particularly valuable because many arthritic patients are reported as having an intolerance for thyroid extract. In our experience this has seldom been noted when clinical signs and symptoms of hypothyroidism coexist with arthritis.

Arthritis and Hypopituitary States.—The anterior pituitary is a source of growth hormone and experimental work has shown that growth hormone exerts a specific proliferative action on cartilaginous tissues of the joint structure.

In *acromegaly*, which is associated with excessive growth hormone production, hypertrophic changes occur in the articular surfaces. Atkinson states that in acromegalic cases "every bone may be abnormal in shape and appearance and all the bones concerned in the formation of the joint may show signs of rheumatoid arthritis." When dealing with hypertrophic arthritis of acromegaly due to a hyperfunctional eosinophilic pituitary state, *estrogenic therapy* is administered in quantities

sufficient to suppress or inhibit the pituitary eosinophilic hyperfunction. The best therapeutic results are obtained in acromegalic cases in the climacteric age.

A similar therapeutic procedure is the administration of estrogenic substance in large dosage and over extended periods to depress the anterior pituitary prolactin production and the abnormal quantity found in the blood of menopausal women. It has been shown that menopausal symptoms persist while prolactin is present in the blood, and that estrogen administration in adequate quantities is required before symptoms are relieved and the prolactin disappears. Menopausal signs recur when the prolactin reappears in the blood after estrogenic therapy is discontinued.

Children in the pubertal ages with Fröhlich's syndrome, which is considered by some to be a deficiency of the anterior pituitary and thyroid glands, sometimes complain of pain in the hip and knee regions. x-Ray examination may reveal some roughening of the epiphyseal areas in the femoral head or neck but, more commonly, a slipped epiphysis is observed. The subjective arthritic symptoms result from this nonarthritic pathology.

Anterior pituitary deficiencies *per se* have no apparent primary relationship to arthritis. We have referred to the role of the anterior pituitary as the cause of secondary hypothyroidism. Its chief importance is as a cause of obesity which may complicate the arthritic state.

In the majority of hypopituitary cases we depend upon the oral administration of anterior pituitary extract in total dosage of from $1\frac{1}{2}$ to 3 grains daily, given in divided doses immediately after meals. Hypopituitary cases generally have a coexisting secondary hypothyroidism, consequently thyroid extract is also administered in dosage which is from one fifth to one fourth of the total amount of anterior pituitary extract administered. The popular theory is that orally administered anterior pituitary extract is devoid of therapeutic action. Our clinical experience with orally administered anterior pituitary extract is to the contrary, and numerous accredited and clinically experienced endocrinologists support our view that oral administration is efficacious.

For those who desire a more rapid therapeutic action from the anterior pituitary preparation, the use of Collip's combined anterior pituitary fractions, commercially available as Polyanyn, by hypodermic is recommended. This should be administered in 1-cc. to 2-cc. doses two or three times a week.

SUMMARY

Endocrine disorders, essentially deficiency states, are observed in a calculable, though minor, percentage of all forms of arthritis. The menopausal state, induced or natural, accounts for the major percentage and the hypothyroid states for the minor percentage of endocrine disorders present in arthritis. In both the degree of the hormone deficiency is the most important factor. The specific hormonal deficiency manifestations are the first to be affected by endocrine therapy, the arthritic state the last to be relieved. In a personal communication of recent date, Hall states: "As I look back on my experience, I am perfectly sure that some of these patients with low metabolic rates who improved on thyroid were patients with ovarian deficiency states and not thyroid deficiency states. However, I do still feel that a good many patients with arthritis have a thyroid deficiency and that a good many patients with arthralgia have myxedema."

While the osseous pathology of arthritis is not changed by endocrine therapy, the patient's metabolism and the cell and tissue fluid exchange is reestablished to normal level. The range of dosage and duration of therapy are in direct relationship to the existing hormone deficiency.

Reference has been made to the interpretation by Maranon of the disturbed endocrine interrelationship in menopausal patients with *obesity and arthritis*. This may be considered as the secondary aspect of the primary endocrine deficiency. Both the clinical and therapeutic phases, as well as the interpreted pathophysiologic aspect of arthritis, must be evaluated to establish sound principles for endocrine therapy in arthritis. Equally, certain basic principles of endocrine therapy also apply, namely that endocrine therapy will be effective only to the extent of the existing endocrine deficiency.

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GALLBLADDER INFECTIONS AS A FACTOR IN ARTHRITIS

Four problems immediately present themselves in a study of the possible relationship of gallbladder infection to arthritis: (1) Is the gallbladder a common focus of infection? (2) Is there proof, either experimental or clinical, that removal of this focus is beneficial in arthritis? (3) Are there readily available methods for making a clinical diagnosis of gallbladder infection? (4) Are there satisfactory nonsurgical methods of treating gallbladder infection?

The Gallbladder as a Focus of Infection.—There is ample proof that infection frequently is associated with gallbladder disease. Various workers have reported positive cultures from gallbladder bile at operation in from 19 to 54 per cent of cases, and from the wall in from 25 to 84 per cent. Rehfuss and Nelson state:¹ "In a composite view of 2,162 cases of cholecystitis studied bacteriologically following cholecystectomies, more than 45 per cent yielded positive cultures from the gallbladder wall, more than 29 per cent from the contents of the gallbladder. . . . In general, from this study, we are inclined to believe that almost one-half of the cases of gallbladder disease seen clinically are bacterial in origin." Positive cultures are most frequent in acute cases and in those with calculi.²

Bacteriologic reports have shown streptococci, staphylococci, and colon bacilli most frequently, although many other organisms have been reported. These may originate in the mouth and upper respiratory tract or in the bowel. The schematic representation of Rehfuss and Nelson illustrates these possibilities (Fig. 201).

It therefore seems likely that the gallbladder may act as a focus of infection. As with other foci, there is considerable

controversy as to the importance of these lesions in arthritis. Judd and Hench³ reported gallbladder infection in 5.7 per cent of 124 cases of chronic infectious arthritis. They believe that, in some cases, the cholecystitis and arthritis may bear an indirect relationship, both arising from some other primary focus. In other cases it appears that the gallbladder may act directly as a focus. Experimental work has shown the presence of organisms capable of reproducing arthritic lesions in animals. A follow-up study of 46 cases of atrophic arthritis in which cholecystectomy had been performed showed complete relief of the arthritic symptoms in five cases, marked improvement in eleven, and moderate improvement in eight—a total of 52 per cent improved by operation. These writers conclude

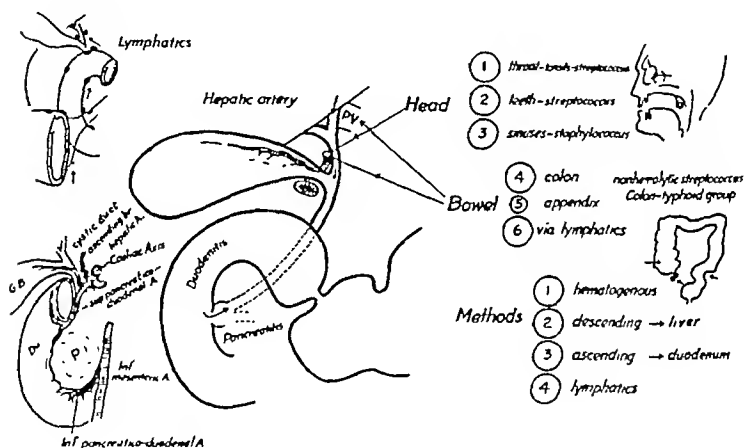


Fig. 201.—Possible sources of biliary infection.

that "when definite surgical indications for cholecystectomy are present, it is justifiable to urge surgical intervention in the hope that the arthritis may be definitely benefited."

Other writers^{4, 5} agree that, while the incidence of gallbladder disease is probably no higher in arthritis than in routine hospital or clinic admissions (about 5 per cent), removal of an infected gallbladder may have a *beneficial effect* on infectious arthritis.

Diagnosis of Gallbladder Disease.—**CHOLECYSTOGRAPHY.**—The diagnosis of gallbladder disease has been greatly facilitated by the use of cholecystography, and it is undoubtedly justifiable to look with suspicion upon any gallbladder which shows *faulty visualization* or *disturbed emptying*. How-

ever, disturbed function does not necessarily mean advanced disease, nor does it indicate infection.

BILIARY DRAINAGE.—In our experience *transduodenal biliary drainage* has been of great assistance in clarifying the diagnosis and also in obtaining some information regarding the bacterial content of the bile. In a considerable experience with diagnostic biliary drainage, it has been found possible by this procedure to clarify the diagnosis in those cases which show absent or poor visualization or suspicious stone shadows by oral cholecystography. About a third of these patients prove to have normally functioning gallbladders upon further study, another third give evidence of cholelithiasis, while the remainder continue to fall into the class of nonfunctioning gallbladders, most of which at operation show extensive cholecystitis with or without stones.⁶

The findings upon which a diagnosis of gallbladder disease may be made by duodenal tube are the absence of a normal gallbladder fraction of bile (B bile of Lyon), the presence of bile-stained mucus, pus cells or columnar epithelia, and the presence of calcium bilirubin pigment, cholesterol crystals, or both.⁷ Evidence of poor function (scant or absent B bile) associated with signs of catarrh and exfoliation (mucus, pus, and epithelial cells) may be quite transient, and such cases may later show normal function both by tube and x-ray. These findings would not seem to represent sufficient disease to be of importance in considering focal infection. Cases with suggestive evidence of *stone* (calcium bilirubin pigment, cholesterol crystals or both), regardless of the degree of dysfunction or inflammation, must be looked upon with suspicion and those with complete nonfunction, even without evidence of calculi, are undoubtedly diseased and are commonly infected. In order to obtain conclusive findings it is often necessary to repeat the drainage one or more times. The technic must be standardized and carefully followed in every instance. It is essential that the material be examined by an *expert microscopist*. Lacking any of these qualifications, one should not attempt to draw conclusions from this procedure; under these conditions, however, we have found biliary drainage to be of great value in clarifying the diagnosis.

Problem of Demonstrating Infection by Duodenal Drainage.—The problem of demonstrating infection by duodenal drainage is far less satisfactory. As stated above, operative studies have shown positive cultures from gallbladder bile only about half as frequently as from the wall.⁸ Barring

other complicating factors, therefore, it seems unlikely that more than half of the infected cases could be demonstrated by bile cultures. If one adds to this the obvious inaccuracies of duodenal cultures, the likelihood of correctly diagnosing biliary infection by duodenal drainage seems remote. Practical experience, however, has shown that repeated pure cultures of pathogenic organisms may be obtained that agree with operative cultures in a fair percentage of cases. Whipple⁹ in 1921 found 50 per cent agreement between duodenal and operative bile cultures in twenty-six cases. Hanssen and Yurevich¹⁰ studied forty-eight patients both preoperatively and at operation and found agreement of cultural findings in 54 per cent. Contamination was present in the duodenal cultures in 46 per cent. Lyon¹¹ reported that in a "majority" of patients coming to operation, the surgical cultures agreed with preoperative drainage cultures.

Twiss and his associates⁸ recently have reported results of cultures taken by means of a *special duodenal tube*, the opening of which is encapsulated to prevent contamination by oral and upper respiratory organisms. In a series of 120 operative patients with biliary disease, sterile cultures were obtained in seventy-five cases by this means (63 per cent); seventy-four of these were sterile by operative culture. Positive duodenal cultures were obtained in twenty-eight cases, in twenty-five of which the same organism was found at operation. Positive cultures were obtained preoperatively in seventeen patients having sterile cultures at operation. In other words, preoperative cultural findings were confirmed at operation in 83 per cent of the cases. This report suggests a distinct advantage in the encapsulated tube method when the incidence of sterile cultures (63 per cent) is compared with previously reported series of Garbat (38 per cent), Whipple (15 per cent), and Lyon (15 per cent).⁸

Interpretation of positive cultures is extremely difficult. Certain organisms are rarely if ever found in the bile at operation. These include *Micrococcus catarrhalis*, *Pneumococcus*, *Friedländer's bacillus*, and *Staphylococcus albus*. The presence of any of these organisms in duodenal cultures therefore suggests *oral* contamination. Mixed cultures are also uncommon in operative bile, so that the presence of multiple organisms suggests contamination. However, the presence of known pathogens (*Streptococcus*, *Staphylococcus aureus*, *Colon bacillus*, etc.) in pure culture in two or more drainages is suggestive evidence of infection. This is particularly true if

the x-ray and biliary microscopic findings suggest biliary disease.

Cultural Findings in Twenty-nine Cases.—A review of the cultural findings in the last twenty-nine consecutive cases of arthritis with abnormal cholecystograms is shown in Table 1. Cultures were obtained during routine drainages without any special preparation. Care was taken to obtain the specimens from a part of the tube not grossly contaminated and while bile was flowing freely. This was done by introducing a sterile needle into the tube well above the end at which manipulations had been carried out, and aspirating the bile slowly so as to prevent regurgitation from the contaminated area.

TABLE 1
CULTURES OF BILE OBTAINED BY DUODENAL TUBE

	Number of cases.	Per cent
Total number of arthritic patients studied.....	29	
Patients showing negative (sterile) cultures (first examination).....	13	45
Patients showing positive cultures (first examination).....	16	55
Patients showing obvious contaminations.....	6	20
Patients showing pathogenic organisms.....	10	34.5

Organisms.	Cases.	Gall-bladder disease.	Gallstones present.	
			Definite.	Questionable.
<i>Bacillus coli</i> (alone or combined).....	4	4	2	1
<i>Streptococcus viridans</i>	1			
<i>Staphylococcus aureus</i>	2	2	..	1
<i>Salmonella</i>	1	1	1	
Nonhemolytic streptococci.....	2	2	1	1
Totals.....	10	9	4	3

Organisms were cultured from the bile in sixteen of the twenty-nine cases, or 55 per cent; thirteen, or 45 per cent, had sterile cultures. Of the sixteen positive cultures, six were considered to be obvious contaminations and included cultures of *Staphylococcus albus*, *diphtheroids*, or *streptococci* in combination with one of these. There were ten cases (34.5 per cent of the entire group) in which possible pathogens were found. These included *Bacillus coli* in pure culture or in combination, *Streptococcus viridans*, *Staphylococcus aureus*, nonhemolytic *streptococci*, and a member of the *Salmonella* group. In these

ten cases, gallstones were definitely diagnosed in four and were suggested by the x-ray in three more. In all ten both the drainage and x-ray showed definite evidence of disease.

Since it is recognized that the chief source of contamination is from the upper respiratory and oral secretions carried through the stomach, it seemed probable that the absence of free hydrochloric acid in the fasting gastric content might bear a relation to duodenal cultures. Table 2 classifies the results in twenty-one cases in which fasting acid figures were available. Of the nine cases without free acid, there were six positive and three sterile cultures; three of the positives were obvious contaminations. There were twelve cases with free acid present in the fasting stomach. In this group there were six positive and six sterile cultures. Of the positives, two were obvious contaminations. In this small series it appears that contamination of the duodenum is more likely in achlorhydria, a finding which agrees with other published work.¹⁴

TABLE 2
RELATION OF FASTING GASTRIC ACIDITY TO DUODENAL CULTURES
(21 cases)

	Cases.	Cultures.		
		Sterile.	Positive.	Contam-ination.
Free HCl present.....	12	6	6	2 (16.6%)
Free HCl absent.....	9	3	6	3 (33.3%)

Treatment.—If, after consideration of all these factors, it is felt that the gallbladder or biliary tract may be a focus of infection, what treatment is advisable? We agree with Judd and Hench and others that in the presence of demonstrable pathology, such as cholelithiasis or complete nonfunction with symptoms, *surgery* is advisable. In those cases not showing definite advanced disease, however, a period of *medical management* may be justified. We have used a low fat diet, cholagogues, periodic therapeutic drainages and autogenous vaccines. In many instances this program has resulted in a return to normal function, decreased evidence of catarrhal exudate and subsequent negative cultures. Several authors have suggested *methenamine*,¹² and recent investigators have shown that *sulfanilamide*¹³ is concentrated in the gallbladder.

Follow-up data are available on only one of the patients in this series, a man of thirty-five with early atrophic arthritis. While the cholecystogram was relatively normal, a history of recurrent mild jaundice suggested the need of further study. Biliary drainage showed evidence of cholangitis, and two consecutive cultures gave a pure culture of *Streptococcus viridans*. The patient was treated with graduated doses of an autogenous vaccine and periodic courses of a choleric.* Subsequently, three sterile cultures were obtained on consecutive drainages. Evidence of cholangitis definitely decreased with a decrease in the serum bilirubin level. During a period of eighteen months there was definite improvement in the arthritic symptoms.

SUMMARY AND CONCLUSIONS

1. From a study of the literature, it appears that the gallbladder, if diseased, is frequently infected and therefore could act as a focus of infection.

2. There are numerous reports of improvement in arthritic patients, especially those with atrophic arthritis, upon removal of a diseased gallbladder.

3. Although gallbladder disease can be inferred when the cholecystogram is abnormal, biliary drainage may be of great value in interpreting the cholecystographic appearances. Biliary drainage is of value only in experienced hands. Demonstration of the presence or absence of infection by biliary drainage is not entirely reliable, but repeated positive cultures of pathogens in the presence of indications of disease by x-ray and biliary drainage is very suggestive evidence. Other workers have shown a high percentage of agreement between duodenal and operative cultures.

4. Medical treatment of biliary infection may prove effective in some cases. Many biliary infections involve the gallbladder wall, and it is therefore questionable whether any medical regimen is adequate for eradication of such disease. In those cases showing definite pathology, surgery should be seriously considered.

5. In a series of twenty-nine arthritics, pathogenic organisms were found in the bile in ten (35 per cent). All of these showed drainage and x-ray evidence of disease, stones being demonstrated in four and suspected in three more.

6. Follow-up studies are reported in a case of atrophic arthritis with *Streptococcus viridans* infection associated with cholangitis.

* Decholin (Dehydrocholic Acid), Riedel de Haen, Inc., New York City.

and endotoxins may be largely eliminated by the use of relatively avirulent strains of bacteria, as well as by the processing of the fractional preparations derived from them.

Bactericidal Chemotherapy versus Immunotherapy.—

The employment of bacterial products in chronic arthritis need not be withheld because of the lack of a proved infectious agent. To withhold such therapy in the circumstances would be about as logical as to refuse to use gold salts in treatment because gold can in no manner be concerned in the causation of this disease. Observations and experience justify the concept that in bacterial products we have very potent agents affecting the chronic forms of arthritis both adversely and favorably, depending upon dosage. Better progress will be made if the subject is approached in this manner, than has been made in the past when every exhibition of a bacterial product has required justification on an etiologic and immunologic basis.

A new field of chemotherapy with bactericidal products isolated from cultures of saprophytic bacteria by Dubos³ and by Hoogerheide⁴ is beginning to be explored. These substances have been purified and obtained in crystalline form. Some are so potent that 0.000,03 mg. when added to 5 cc. of nutrient broth will prevent the growth of pneumococci;³ and 0.02 mg. when mixed with a culture of virulent pneumococci and injected intraperitoneally into mice has protected them against as much as one million lethal doses of pneumococci.⁴

The practice of using very minute doses of bacterial extracts in the treatment of arthritis, as developed over the years since 1929,⁵ may be more nearly in line with this form of therapy than with that based on the building of immunity, or of counteracting an existing hypersensitiveness. The results obtained from minute doses have suggested strongly that there may be a relationship to the methods employed for desensitization, but many of the phenomena encountered are not consistent with this hypothesis.

The haunting ghost of *immunologic* procedure has impeded progress in the treatment of chronic arthritis with bacterial products for two reasons:

1. The demand for "autogenous vaccines" has confused the technic of treatment by introducing for each individual an untried product about which there can be no direct knowledge of dosage requirements. This has done little more than add another variable in a procedure, the success of which depends

upon the delicate adjustment of dosage to the individual's needs.

It is important to emphasize the fact that patients with arthritis react similarly to minute doses of suspensions or extracts of *all* gram-positive cocci, whether streptococci, staphylococci or pneumococci. *Immunologic specificity* does not appear to enter into consideration in this form of treatment, so that a primary simplification of the procedure is that of choosing a standard preparation concerning which something has been learned regarding dosage and reactions.

2. Again, progress has been delayed by the reasoning that each dose in a course of treatment is a stepping stone to the watch tower of immunologic resistance which wards off all evils. It has become almost an axiom that if resistance is to be raised, dosage must be increased. This has rendered it practically impossible to have the physician avoid an increasing scale of dosage, particularly if the patient is doing well. When the patient is doing well under treatment by microdosage, an increase of dosage is especially to be avoided.

Reactions and Responses.—The reactions of the patient in this method have been described fully elsewhere,² and are recognized easily as differing from those elicited by bacterial toxins or by foreign proteins. There is a definite zone of dosage⁶ in which sharp exacerbations of symptoms follow the injections. Immediately above this zonal range, the reactions become less pronounced, are increasingly delayed and vague, and, with higher dosage, fail to appear. This constitutes a paradoxical phenomenon for which no explanation is available. As another means of differentiating this procedure from that commonly used in therapy with bacterial vaccines, it may be stated that these larger doses, administered without evident reaction, are yet very much smaller than those usually used in prophylactic treatment.

A minute dose, for example, may be followed by a sharp exacerbation of the arthritic symptoms in a patient, yet one hundred times this amount may be administered to the *same* patient without visible effect. The latter dose is above that amount to which the patient reacts, and appears, even upon repetition, neither to harm nor to benefit the patient. In direct contrast, the hundredth part of this dose, which was followed by an exacerbation of symptoms, upon repetition is similarly followed by another flare-up, and the patient appears definitely to be harmed by its repeated use.

The importance of the last-named consideration now ap-

pears evident. If dosage is reduced to an amount *below that to which the patient reacts*, ordinarily an amount is determined which is followed by prompt alleviation of symptoms. The patient now enters an euphoric state, which may last for five, seven, or more days. A relapse terminates this euphoria, but repetition of the former dose again typically provides relief. This procedure may be repeated time after time. If the patient is kept constantly in this euphoric state, general improvement occurs. Only after considerable repetition of the dosage providing these periods of relief does their length tend to shorten. This is the sole indication for increasing an established satisfactory dosage.

Technic of Treatment with Microdosage.—The details of the methods with microdosage of bacterial suspensions,¹ and with soluble fractions of bacteria,⁶ are similar. Unfortunately there is no method of estimating the dosage which is likely to be the most effective in a given individual, so that it is necessary to resort to *clinical trial and analysis*.

With *bacterial suspensions*, Crowe¹ recommends a starting dose of one-tenth of a million bacteria. This amount he finds usually produces some very definite effect upon the patient, and permits of an analysis of symptoms so that the dosage can be adjusted upward or downward as seems warranted. He finds that a convenient range of concentration of the vaccines is as follows: 500,000, 50,000, 500, and 50 bacteria respectively per cubic centimeter. The range of dosage usually required in treatment is between 10 (only) and 1,000,000 bacteria.

With the *soluble fractions of bacteria*, it appears more desirable to begin with trial doses of the weakest dilutions, and to raise the dosage tenfold at intervals of four or five days until some reaction is noted, after which the dose should be adjusted just below the amount producing it. If intermediate doses are chosen at the beginning, they are frequently too large and their effects may persist for several weeks, rendering it difficult to appraise the symptoms appearing after subsequent doses.

Analyzing the Results from Trial Injections.—Briefly, there are four conditions which may arise following a trial injection:

1. No change—the patient remains in *status quo*. This indicates that the dosage has been too small.

2. Improvement may occur, beginning within a few hours after the injection. Pain, stiffness and swelling become less. There is a definite feeling of well-being. The interpretation here is that the dosage has been correct, or nearly so.

3. The joints may become worse within the first twenty-four hours. Pain, swelling and stiffness are aggravated. There may also be transient flashes of pain in joints not previously involved. This is referred to as the *focal reaction*, and indicates that the dosage has been too large.

4. The patient may become worse. This is a *general reaction*, with such symptoms as lassitude, drowsiness, inertia, general aching and malaise, headache, anorexia, and possibly a slight rise of temperature. In this instance the dosage has been very much too large.

The procedure to be followed with subsequent dosage in each instance may be summarized:

Trial injection

No. I results in	No change	Improvement	Focal reaction	General reaction
With trial injection No. II	Increase dosage	Maintain dosage	Reduce dos- age	Reduce dosage drastically

While it is impossible to adopt a rule-of-thumb schedule of dosage, its trend may be indicated in a little more detail (Table 1).

TABLE 1
TREND OF MICRODOSAGE IN ARTHRITIS

Trial injection No.	Patient 1.		Patient 2.		Patient 3.		Patient 4.	
	Dos- age.	Reac- tion.	Dos- age.	Reac- tion.	Dos- age.	Reac- tion.	Dos- age.	Reac- tion.
I	x	0	10x	i/2	100x	f/2	1000x	g/3
II	10x	0	10x	i/6	10x to 50x	f/3	10x to 50x	g & f/3
III	100x	0	10x	i/4	x to 5x	f/0.5	0.1x to 0.5x	f/1
IV	1000x	i/4	15x	i/7	x to 5x	i/7	0.1x to 0.5x	i/6

Key to abbreviations: x, 10x, etc. = quantitative dosage. 0 = no reaction; i = improvement, f = focal reaction; g = general reaction; i/2, f/3, g/3, etc. = duration in days of the different phases.

Determining the Dosage after Trial.—If, after a trial injection, no reaction occurs, the dose is increased tenfold after an interval of four to seven days. It may have to be increased

in this manner several times before improvement, a focal reaction or a general reaction results. That amount of the bacterial product which is followed by improvement is a *working dose* and is not far removed from the *optimal* one for the patient. It should be repeated after five to seven days, when one is sure that the interval of improvement has terminated.

Indications for Increasing the Dosage.—The period of improvement after the second dose may be several days longer than was that following the first dose. This may be due to cumulative action. The intervals between doses will be determined by the length of these periods of improvement. Dosage is increased only when, on established constant dosage, the periods of improvement become shorter. *This is the only criterion for increasing dosage in a patient who has been doing well, and success with this method of treatment depends very largely upon its strict observance.*

Significance of Focal and General Reactions.—A very mild focal reaction following an injection is not of much moment, but one in which the aggravated symptoms last more than ten or twelve hours must be regarded as severe enough to warrant reduction of the dosage. The more severe focal reactions may last three or four days, and a reduction to one-tenth the dosage exciting them is desirable. A reduction of 50 per cent is usually sufficient in the milder focal reactions.

The appearance of the symptoms of a *general reaction* is always to be regarded as of more serious consequence, not only because it may harm the patient but also because its effects may last for several weeks and interfere with the interpretation of the symptoms following subsequent injections. One one-hundredth of the amount exciting it may be injected after seven days. A second such reduction may be required before dosage is lowered to an amount approaching the patient's needs.

The symptoms of the general reaction are not as outstanding as those of the focal reaction, and the patient may not mention them. Unless these are brought out by direct questioning, failure in treatment from overdosage will result.

Adjusting the Dosage to Stated Intervals between Treatments.—If weekly intervals are used in treatment, the ideal dosage of the bacterial product is the *smallest amount* which will be followed by a period of relief lasting seven or more days. This amount is repeated week after week until it fails to be followed by seven days of relief. This is indicated by a recurrence of symptoms just before the patient is due for the next injection of the course. The occurrence of this relapse is the

cue for increasing an established dosage. The amount of the increase may be safely set at 50 per cent increments. If the first increase does not reestablish the former period of improvement, another may be undertaken at the time of the next injection.

These *increases* to maintain the periods of improvement become necessary at varying intervals in different patients. As the patient improves gradually through the months of treatment, the intervals between injections may usually be increased, so that ten, fourteen, twenty-one, or even twenty-eight days come to be used. With this improvement relapse phases no longer appear, as the effects of individual doses are dissipated. Cessation of treatment at this stage is followed by an actual reactivation of the arthritis, usually at the end of two or three months. Because of this it has become the established practice to continue the treatments at intervals of twenty-one to twenty-eight days for at least a year after it is reasonably certain that the arthritis has become inactive.

Summary.—Theoretical considerations and a practical method of employing microdosage of bacterial products in the treatment of chronic arthritis have been presented.

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SPECIAL THERAPEUTIC AGENTS IN ARTHRITIS

Attitude of Patient and Physician.—The conviction that *nothing can be done* for the chronic arthritic seems to have been accepted by a great many members of the medical profession and the public generally. This impression has arisen probably from several causes, among them the unknown etiology, the chronicity of the disease, and the attitude of the patient himself.

The *chronicity* of atrophic and hypertrophic arthritis has contributed to the hopeless attitude so frequently adopted. The management of arthritis requires an infinite amount of patience and understanding of each individual patient and his problems, as well as a great deal of time and attention to apparently insignificant details on the part of the physician called upon to solve one of these problems.

The *attitude of the patient* toward his disease has contributed in no small amount toward fostering this hopeless attitude. The average arthritic, during the early stages of his disease, is endowed with a minimum of *expectation*, and a maximum of *suspicion*.

The Basis of Treatment in Arthritis.—Before attempting the treatment of arthritis, a clear picture of the various manifestations of the disease is necessary.

Bearing in mind the widespread nature of the process constituting arthritis, it is not logical to expect the administration of any *single* therapeutic agent to effect a cure. If it can be proved that there is a single etiologic agent which persists long enough to be attacked, then it is logical to expect someone to discover a single agent that will reverse the process. Apparently such proof is not at hand, so that, at present, treatment must be directed at the disturbed physiologic functions as they are found.

The Multiplicity of "Cures."—Numerous agents have been hailed as being specifics in arthritis, and many are advertised and sold under the claim of giving great benefit in most cases of the disease. Hardly a day passes without the appearance in the physician's mail of advertisements for some new drug, or some detail man smiles his way into the office with samples "to try on a few of your worst cases." Carefully chosen excerpts from physicians' articles are presented, distorting the context of the original. Unfortunately, the benefit from the vast majority of such products goes to the manufacturers, not to the arthritic patients.

Difficulties in Evaluation of Results from Therapeutic Agents.—There are several difficulties encountered in the critical evaluation of results in a series of cases used to test the value of any therapeutic agent, most of the difficulties arising from the *unpredictable nature* of the arthritic process. These factors must be given due consideration in judging the value of the agent under observation.

The first of these is the frequency with which *remission* occurs in the course of the disease, regardless of treatment or lack of treatment. It is characteristic, and it is utterly impossible to predict in any given case at any given time whether the next week will mark the beginning of an exacerbation or a remission. Consequently, it is a great temptation to credit the latest type of treatment with having produced the remission. Long follow-up periods are, therefore, necessary before it can be accurately said that anything more than a natural remission has occurred.

The second item to remember is the fact that, in many reports, patients were started on an entirely *different* regimen than that to which they were accustomed, at the same time they started on the agent to be tested. Then, at the end of the study, it is not possible to determine which produced the results.

The third item is the elasticity of the word "*cure*" as frequently used. Some concrete measure of improvement must be used, as size of joints, sedimentation rate, and range of motion.

The fourth item is the matter of *controls*. This has been, for a long time, the great criticism of many persons justly skeptical of published reports. Probably exact control in any series of arthritic cases is impossible, but certainly nothing can be proved by testing arbitrarily the first twenty-five or fifty patients admitted to the clinic, regardless of type, pres-

ence of complications, activity or stage of development of the disease; nevertheless, several reports have been based on just such series. Neither does treating every other patient in a series with the agent to be tested and the others with an inert solution constitute adequate control. Such procedures disregard the variable causes and unpredictable nature of the disease, as well as the possibility of including in the series patients whose disease had advanced to the stage of invalidism, where no agent can logically be expected to produce any benefit.

Probably the nearest approach to adequate control lies in *proper selection*. Patients to be given any treatment which is being studied critically should be observed while on a *constant regimen* for a period of at least four months, given the material to be tested while kept as nearly as possible on the same program, and then followed up for a period of two years. Deviation from the program as originally set up during this two-year period should be noted. In selecting patients for a test of this sort, care should be exercised to see that only the type of disease to be studied, and only those patients in whom the disease process appears to be reversible, are included in the series. This management of control is probably still not perfect, but under the circumstances it is the best that can be done.

THERAPEUTIC AGENTS EMPLOYED IN ARTHRITIS

Any special agent for the control of arthritis that remains popular after a ten-year period of trial is deserving of special attention. Seldom does an agent last that long. However, gold salts have survived that period, and seem to grow increasingly popular.

Gold Salts.—Since Forestier's work in France several years ago, gold has been enjoying increasing popularity in Europe. In the past six years, it has become a rather popular agent in the United States, and numerous reports have appeared pro and con.

There are several preparations of gold that have been used in this country, some for *intramuscular* and some for *intravenous* administration. Apparently the intramuscular route is to be preferred because reactions seem to be fewer and the results as good as obtained by the intravenous route. The great majority of the reports deal with products intended for intramuscular use. Among them may be mentioned *Myochrysine*, *Allochrysine*, *Sanocrysine*, *Solganol-B* and *Parmanil*. There may be minor differences in toxicity and therapeutic

effects, but for discussion they may be conveniently considered as a group.

Opinion is divided regarding the value of gold salts for therapeutics, with perhaps a slight majority of reports favoring it. A great many reports are indefinite as to diagnosis of the types of arthritis treated, some neglect to mention the length of time patients were treated, and some lacked adequate control. Men such as Key, Stone and Snyder are of the opinion that gold is a valuable therapeutic agent for atrophic arthritis. Key¹ says: "It is our opinion that gold therapy has definitely ameliorated the course of the disease in the majority of our patients with atrophic arthritis in whom it has been given a fair trial, and this is true regardless of the duration of the disease." On the other hand, results of Thompson, Wyatt and Hicks² were "disappointing."

Recently Ellman and Lawrence³ performed an interesting experiment in an attempt to solve the problem of controls and establish some criterion for measuring improvement. They treated three groups of twenty patients each, one with sterile oil, one with small doses (maximal dose 100 mg.), and one with large doses (maximal dose 200 mg.) of gold. Results are given in Table 1.

TABLE 1
RESULTS FROM GOLD THERAPY, EXPRESSED IN PER CENT

	Large doses of gold.	Small doses of gold.	Sterile oil.
Cured.....	50	30	5
Improved.....	45	60	65
Not improved.....	5	10	30
Joint swelling reduced...	81	79	16
Sedimentation rate reduced to normal....	74	40	15

Ten times as many patients were cured by large doses of gold as by the control dose of oil, and six times as many by small doses of gold. This is definitely a step in the right direction in the matter of controls, but is by no means perfect. It is an attempt also to establish some criteria by which improvement can be measured, rather than being content with the vague terms "cured," "greatly improved," and the like so often encountered.

So far, no reports have been found in the literature of any series of cases treated with gold that have quite met the

standards of controls as previously set forth. A series of cases are now being treated at the Abington Hospital Dispensary in which the attempt is being made to set up adequate control as nearly as possible. As yet it is too early in the studies to draw any definite conclusions, but there is notably less enthusiasm on the part of the patients and physicians than existed at the beginning of study.

Reactions.—Unfortunately the administration of gold salts is fraught with danger; reactions are numerous and sometimes rather severe, with even an occasional death. Some of the toxic reactions reported are dizziness, headache, vomiting, diarrhea, abdominal pain, stomatitis, jaundice, erythema, herpes, albuminuria, exfoliative dermatitis, purpura haemorrhagica, agranulocytosis and aplastic anemia.

This is indeed a formidable array of reactions, and properly makes one hesitate to subject patients to such hazards without some assurance that they will probably derive some benefit from the treatment.

Once a reaction has occurred, treatment is purely *symptomatic*. Obviously the best method is *prevention* but, so far, no successful methods of preventing reactions have been reported, except the use of caution in the selection of patients and extreme watchfulness while they are undergoing therapy, so that the drug may be stopped at the first sign of reaction.

Before starting anyone on gold, it is the practice in this clinic, besides giving a careful physical examination, to see that each patient has the following *laboratory work* done: routine urine examination, complete blood count, nonprotein nitrogen test, some test of liver function, and of renal function, platelet count, and determination of the sedimentation rate. Each week before the patient is given his injection of gold he is given at least a routine urine examination and white blood count, and a hemoglobin determination is made; in addition, his mouth and his skin are examined and a careful inquiry is made for symptoms of any reactions. Every three or four weeks a nonprotein nitrogen estimation and platelet count are made. At the first sign of reaction, treatment is stopped for about a month and then resumed cautiously in smaller doses, for skin reactions have been reported as occurring as much as six weeks after treatment. Fewer immediate reactions, such as flushing and giddiness, will be encountered if the patient is given his injection *lying down* and required to remain in that position for ten minutes afterwards.

Contraindications.—Persons with definite hepatic and renal

disease (80 per cent of gold is excreted through the kidneys), eczema, colitis, or a history of purpura should not be given gold therapy.

Sulfur.—This agent seems to have about run its course and is apparently headed rapidly for oblivion. The Council on Pharmacy and Chemistry of the American Medical Association,⁴ in a critical review of the literature on sulfur, concluded that it is of very questionable value: "It would seem to be of great significance that not one of the leading arthritic clinics of the United States has adopted the use of sulfur in the treatment of arthritis, so far as can be determined."

Bee Venom.—The infrequency of rheumatism among bee-keepers is often mentioned in works devoted to the trade of raising bees, although no one seems actually to have made a scientific study of the matter. However, this method of therapy has captured the fancy of the public, and many a patient has "just heard of someone who was cured of arthritis by bee stings." But reports of the use of bee venom in the literature have been disappointing—many investigators stopped using it because it was so *disagreeable* to patients, and still produced no noteworthy effects. Some investigators used one of the various products for intradermal injection, and some used actual stings of bees. Results were equally bad in both cases.

Recently Ainlay⁵ used bee venom intradermally over affected joints, and noted that beneficial effects were obtained mostly in the extra-articular manifestations of the disease, such as "muscular rheumatism, sciatica, lumbago, and neuritis." He concluded that the benefit was due to vascular dilation, and states that "it may be considered as having an effect similar to heat and massage, except that the effect is more lasting." It should be noted, however, that in this series of thirty-seven patients, there was no selection or control attempted—"they were unselected and represent the patients as they came to our clinic." And further, agreeing with Pember-ton that "arthritis is not entirely a disease of joints" . . . careful consideration was given to diet, vitamin intake, rest, and freedom from worry and exposure—measures which in themselves are sufficient to produce remission of symptoms in a large proportion of arthritics, without the addition of bee venom or any other agent.

However, bee venom may have a place in a well-rounded program for some patients, if it is used with the conviction that it is a counterirritant and probably nothing else.

Chaulmoogra Oil.—This remedy has not gained a great deal of popularity, probably because of the considerable pain incident to the injection and the frequency (5 per cent) of abscess formation at the site of injection, together with rather poor results. There are several reports which condemn its use. However, Stanley⁶ is of the opinion that relief of symptoms may be produced by its use. He proposed two hypotheses to account for its efficacy: (1) bactericidal potency, and (2) influence on retention of calcium. Regarding these hypotheses, it should be noted that (1) nobody has proved that arthritis is a bacterial disease and (2) there is no disturbance in calcium metabolism in the circulating blood in arthritis.⁷

Sulfanilamide.—There seem to be no favorable reports concerning the use of sulfanilamide in the treatment of atrophic and hypertrophic arthritis. Bauer and Coggeshall⁸ conclude that "the agent responsible for rheumatoid arthritis is not susceptible to this type of therapy." It has been used at the Abington Hospital in a few scattered cases suspected of being *gonorrheal* in origin, without any appreciable effect. However, if the patient is seen early, while the gonococcus is still active, sulfanilamide is probably the treatment of choice. But such cases are not seen very frequently.

Artificial Jaundice.—Several clinicians have noted independently that the spontaneous development of jaundice in arthritic patients produces a definite remission of joint symptoms. Attempts have been made to reproduce this effect by deliberately producing jaundice in arthritic patients by various methods. Hench^{9, 10} attempted to produce this effect by giving bile salts by mouth, synthetic bile salts by stomach tube, and transfusion of jaundiced blood; he even induced jaundice in one patient by the use of toluylenediamine. In none of these patients was any marked relief of symptoms produced. Thompson and Wyatt,¹¹ however, found that a combination of bilirubin and bile salts given intravenously according to their technic helped materially in alleviating symptoms in atrophic arthritis, although neither agent alone produced the same effect. The introduction of bile salts by iontophoresis was tried on several atrophic arthritics at Abington Hospital, but failed to produce any effect further than a local hyperemia at the site of administration.

These investigations open another very interesting field for research—there seems to be a difference between spontaneous jaundice and jaundice produced by the methods so far attempted. Perhaps an agent, if found, that will produce a

jaundice similar to the spontaneous type, will change the present concept of the treatment of arthritis; at any rate, this subject is deserving of considerably more study.

Vitamin D.—Massive doses of Vitamin D have recently been used in the treatment of arthritis. Bauer and Abram¹² made a most excellent study of this method of therapy in a group of eighteen arthritics, using Drisdol and crystalline Vitamin D in propylene glycol administered in milk. This study is especially significant in that they chose "only those patients whose clinical course has been known for months or years on a constant regimen prior to the institution of any so-called therapy." Results were evaluated from subjective and laboratory data, and the conclusion reached that "the administration of Vitamin D in rheumatoid arthritis is of little or no value in altering the course of the disease. The general effects of the larger doses do not appear significantly different from those observed with the usual therapeutic dose, and do not justify the expense or dangers involved."

On the other hand, Snyder and Squires¹³ published a preliminary report on the use of "activated ergosterol prepared by the *Whittier method*, a form of high dosage vitamin D," in twenty-three cases of chronic arthritis, of which eight were atrophic, eight hypertrophic and seven mixed or borderline cases. They selected their patients from a group that had been under treatment at their clinic for two or three years, and had been uninterruptedly on treatment for at least four months. They concluded that the "administration of this drug has benefited the great majority of these patients in varying degrees." Snyder contends that there is a vast difference between Vitamin D prepared by the Whittier method and the other Vitamin D products prepared by ultraviolet radiation of ergosterol and subsequent extraction of the vitamin by means of alcohol. It is claimed for the Whittier method that, while much less of the finished product is obtained from a given amount of ergosterol, it is a much "purer" product, which is less toxic and more beneficial.

Hence, while these two reports are dealing with Vitamin D in high-dosage forms, they are actually dealing with two different products. Whether or not, in the final analysis, these products will prove of value remains to be seen.

COMMENT

Before the term "specific" can be accurately applied to any therapeutic agent, that agent must produce *regular, clinical*

improvement in most patients treated with it. None of the seven special agents discussed has met that requirement, judging from the data available at present. Some of them are worthy of further study, but the remainder do not seem to be. But since 80 per cent of arthritics can be handled satisfactorily by treatment along broad general lines directed at underlying disturbed physiologic processes, the general use of products which are often dangerous, and which are not definitely proved to be of value, does not seem to be justified. Their use, therefore, should be restricted to research clinics where they can be properly studied and evaluated, and undesirable effects guarded against.

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THE PREVENTION AND CORRECTION OF DEFORMITIES IN ARTHRITIS

Prevention through Proper Splinting.—The subject of prevention and correction of arthritic deformities is of interest not only to the orthopedic surgeon who usually is consulted when deformity has become evident, but is of great importance to the general practitioner as well. The family physician, who treats most cases in the early stage, is in position to prevent deformity by the simple procedure of *proper splinting*. Prevention cannot therefore be overemphasized as splinting is easily done and is almost always successful. On the other hand, deformity, once established, is most difficult to correct; it leads to much time loss, expense and discomfort and never yields as good a joint as can be obtained by splinting. When one considers the neglected patient who, for want of plaster of Paris forearm or leg splint, has developed deformities rendering both hands useless and flexion deformities with perhaps subluxation of the knee joints, the importance of prevention is obvious. The orthopedist, working to correct such a condition, may require two or three years, utilizing measures from wedge casts to the difficult operation of arthroplasty. The patient suffers unnecessarily and much money is spent—all for the want of an ounce of prevention. And again we must point out that the corrected case never secures as good a result as the one in which deformity was prevented.

Types of Arthritic Deformity.—The two chief forms of chronic arthritis, namely atrophic and hypertrophic, differ broadly in that the atrophic form is essentially *inflammatory* in nature whereas the hypertrophic form is *degenerative*. Still's disease is a form of atrophic arthritis which occurs in childhood.

Atrophic Form More Apt to Cause Deformities.—The atrophic form is much more likely to result in deformity than

the hypertrophic form; hence it is in this form that prevention is most necessary. Fortunately the immobilization which is necessary to prevent deformity is a most valuable form of local treatment in all types of inflammatory arthritis, ranging from a mild atrophic to a frank septic arthritis. The fear is often expressed that immobilization will result in a stiff joint. Movement in an inflamed joint is much more likely to result in a stiff joint as movement aggravates the inflammatory processes which are the cause of adhesions, both intra- and periarticular, destruction of cartilage, and ankylosis. Children with normal joints of the foot and knee immobilized for two years in plaster of Paris hip spicas in the treatment of tuberculosis of the hip joint do not form adhesions in the normal joints, which are usually none the worse for the prolonged immobilization. Splinting makes the patient much more comfortable, and swelling, effusions, heat and pain subside. Tonic spasm of the muscles stops and the entire part is put at rest.

As the inflammatory process quiets down, the original cast is bivalved and may be removed for physical therapy in the form of heat. Then massage of muscles may be instituted, increasing gradually through muscle setting to active exercise and finally weight bearing. During this period treatment, as considered elsewhere in this symposium, should be employed as indicated in the particular case. As the patient improves and the need for immobilization becomes less, splinting may be gradually discontinued. The use of splints to prevent deformity is most necessary at night as the patient is apt to lie in the positions of flexion deformities when asleep; hence night splints are continued while there is any tendency to deformity.

Causes of Flexion Deformity.—The common practice of *sitting in a chair* during convalescence is a source of many deformities in arthritis. The position assumed when sitting relaxed with the hands in the lap in a chair is the typical deformity of arthritis. The spine, hips, knees, feet, elbows and wrists are flexed. The shoulders are rotated internally and adducted and the forearm is pronated. A chair is therefore a poor place for the arthritic to rest. *Back and knee rests* in bed are also common causes of flexion deformities.

The patient with active atrophic arthritis should therefore be kept in a *fracture bed* (mattress supported by light boards so that there is no sagging). A back rest must not be used if there is involvement of the spine, hips, or shoulders; instead, the entire bed may be tilted by raising the head of the bed.

Light plaster splints or bivalved casts, as indicated, are used on the involved points.

Position in Which Joints Should Be Splinted.—The position in which the various joints should be supported is of importance as cases are not infrequently seen in which they have been splinted in poor positions. The *spine* should be supported in extension as the deformity assumed is flexion in both atrophic spondylitis and spondylitis ankylopoetica. In mild cases the fracture bed with no pillow may suffice. In the more severe cases a bivalved body cast in extension is indicated. Involvement of the cervical spine is treated by the use of the posterior plaster shell, including the head and neck. In all cases of spondylitis a well-fitted body cast or celluloid jacket in extension should be worn for a long period after the acute process has subsided, as progressive kyphosis and ankylosis are very common. In the cervical spine a jury mast with occiput and chin-brace is necessary. As soon as the arthritic process is sufficiently quiescent, muscle setting of the erector spinae mass (contraction of muscles without moving joints) should be done five minutes every hour to preserve the muscle power of the spinal extensors. Later, when tolerated, active extension exercises of the spine are indicated. In the case of the spine, prevention is particularly important as many cases progress to bony ankylosis, which makes correction impossible. Spinal deformity in flexion not only results in orthopedic disabilities but interferes with proper thoracic expansion and causes a general visceroptosis.

Arthritis of the *temporomandibular joint* is best splinted by the use of an elastic strap passing under the chin and attached to a cloth skull-cap. A diet which does not require mastication is prescribed and exercises of muscle setting, followed by active exercises as the process subsides.

The *shoulder joint* should be supported in 80° abduction, 135° external rotation, and the abductors and external rotators exercised as indicated. The *elbows* are supported in 135° flexion and midrotation of the forearm, with pronation and biceps exercises; the *wrists*, in 135° extension (dorsiflexion) with the fingers and thumb semiflexed and the thumb in opposition (position assumed by normal hand in grasping a cylinder about 2 inches in diameter). The function of the wrist dorsiflexors and the flexors and extensors of the fingers should be exercised. The splinting of the joints of the upper extremity is done by the use of bivalved casts or a plaster splint with a cross-piece of wood to prevent rotation and supported by sandbags.

The *hip joint* is splinted at 180° extension and 20° abduction in midrotation. This may be accomplished by means of a Buck's extension or a plaster cast from the gluteal fold to the toes, or a splint with a wooden cross-bar under the ankle to prevent rotation. If a Buck's extension is used, the traction should be attached well above the knee in order to avoid stretching the knee joint. The abductor and extensor muscle of the hip should be exercised. The *knee* and *foot* are supported with the above type of splint, the knee being held in 180° extension and the foot in 90° dorsiflexion. The quadriceps in arthritis of the knee and the dorsi- and plantar flexors of the foot should be exercised.

In the above, the muscles specifically mentioned to be exercised are those which combat the usual deformity of the part. All muscles should be exercised as much as possible *without exciting the arthritic process*. This is important in even the severely damaged joints, as muscle power is essential to joint function and can only be preserved by use. In the case with marked muscle atrophy there is insufficient power to work a normal joint. The mildest exercises consist of muscle setting, gradually increasing through assisted active exercises in which the part is moved by the patient assisted by the nurse; free active movement of the part follows, and finally, weight bearing.

Pathologic Factors in Correction of Deformities.—To understand the methods of correction of deformity a knowledge of the pathology is essential. An outline of the pathology follows:

Atrophic Arthritis (Rheumatoid, Proliferative or Chronic Polyarthritis).—

The pathologic process is fundamentally *inflammatory*. Round-cell infiltration of the synovial membrane is followed by proliferation of granulation tissue along the margins of the articular cartilage. This tissue forms a thin layer or pannus which grows out over the cartilage. The cartilage under the pannus is absorbed. Vascular granulation tissue forms in the marrow of the epiphyses, extending up to the articular cartilage which may be destroyed.

The changes in the articular cartilage may progress to destruction of the cartilage, with replacement by bone and bony ankylosis resulting. In the less severe cases, adhesions of the cartilage or synovia occur, resulting in fibrous ankylosis or limitation of motion by intra-articular adhesions. The joint capsule thickens due to fibrous tissue formation with the usual tendency of scar tissue to contract, thus further limiting motion. The changes in the musculature of the joint consist of atrophy and, if the joint is allowed to lie in malposition during the disease process, contractures occur in the flexed muscles while continued stretching of opposing muscles results in weakening of the extensors. For example: In the knee, persistent flexion results in contractures of the capsule and hamstrings. The patella becomes fixed, and the quadriceps is weakened by stretching and works at a mechanical disadvantage. Then the fixed patella is unable to oppose the hamstrings. Hence dislocation

occurs. Among the contractures which occur in the periarticular structures are contractures of the vessels and nerves. Old cases of severe flexion contracture of the knee may have sufficient contracture of the vessels and nerves to render any attempt at rapid extension very dangerous. Paralysis or obstruction of the blood supply may result.

Hypertrophic (Osteoarthritis or Degenerative Arthritis).—This is fundamentally a degenerative process rather than an inflammatory one. Degenerative changes occur in the margins of the articular cartilages which are followed by osteophyte formations. In the senile forms, arteriosclerosis and long-continued wear and tear are factors. Continued mechanical injury, such as semilunar tears, joint mice, postural strain, malalignment following fracture or intra-articular fracture, distortion of the femoral head due to Perthe's disease, or slipped epiphyses, are important causes of this type of osteoarthritis. Needless to say in these types of traumatic origin, due to or complicated by torn semilunar cartilages, joint mice, or hypertrophied villi which may block the joint, the loose body or torn cartilage should be removed. The occurrence of arthritic changes in the knee secondary to a torn semilunar cartilage is a strong argument for the removal of all such torn cartilages. Mixed forms of arthritis occur in which rheumatoid and osteoarthritic changes are present in the same case.

Changes in the articular cartilage consist of thinning of the cartilage and fibrillar degeneration. Fibrous tissue replacement may occur. The cartilage in the weight-bearing areas of the joint may disappear, the exposed bone becoming eburnated. In the peripheral portions of the articular cartilage and the perichondrium, proliferation occurs forming osteophytes. Osteophytic formation may limit movement of the joint; however, complete ankylosis does not occur. Hypertrophy of the synovial villi occurs in the later stages. Polypoid processes of the hypertrophied villi or detached villi may cause locking or pain by being caught between the articular surfaces. The capsule and peri-articular structures are little affected.

Chronic villous arthritis usually occurs in women that are "fair, fat and forty." The knees show an hypertrophy of the synovial villi. Some cases progress to osteoarthritis.

Active Inflammatory Processes Contraindicate Corrective Procedures.—Proceeding to the consideration of the correction of deformity it must be stressed that no measure of correction may be employed in the presence of active inflammatory processes in the joint. It is readily seen therefore that the arthritic joint of *traumatic* origin is more suitable for correction than the rheumatoid joint.

The joint should be *quiescent* for several weeks before attempting correction by gentle manipulation and repeated splinting. The period of quiescence before attempting wedge casts should be three to six months, while surgery should not be used unless inflammatory processes have been absent for from six months to one year.

Before proceeding with surgical corrective measures, weakened muscles must be built up by *massage, muscle setting and exercises*. Surgery upon the joint structures or periarticular

tissues results in a local reaction and some adhesion formation. The muscles must be sufficiently powerful to move the joint after obstructions are removed surgically.

Measures to Correct Deformity and Restore Function.

—The following measures are useful in the correction of deformity and restoration of function in the arthritic joint. These measures may be used *singly* or in *combination*:

Repeated gentle *manipulation*, *active exercises* and *splints* are effective measures in the *mildest* cases. The active exercises should consist of forceful contractions of the muscles which tend to correct the deformity present. The exercises are done five minutes every hour. Manipulation should be done gently at least once daily. The splints should be changed every time a gain is made to retain the gain.

Manipulation under general anesthesia is a *dangerous* procedure in rheumatoid cases. It is of value chiefly in joints which have limited movement due to periarticular adhesions following acute trauma. Hypertrophic arthritis with limitation of motion due to osteophytes is not aided by manipulation. One may fracture the osteophyte and produce a loose body in the joint. An occasional case may be benefited by manipulation but, as a rule, deformity may be corrected more safely by means of wedge-casts.

Wedge-casts are of value in the correction of deformities of the joints of the *extremities*. Description of this method as applied to the *knee joint* will illustrate the method: A circular plaster cast is applied from the groin to the toes. When the plaster is sufficiently hardened, it is cut through transversely 2 inches above the knee joint, except for the most anterior 2 inches of circumference. This portion is left to act as a hinge. A cast spreader is used to spread the cast posteriorly, thus extending the knee. The gain in extension is retained by insertion of a wedge of wood between the edges of the cut cast. The block is retained in position by a layer of cotton sheet wadding covered by a thin layer of plaster. The size of the wooden wedge is increased about every five days. This measure is very valuable as serious deformities may be corrected and, if used judiciously, no harm should be done.

The operation of *tendon lengthening* and *capsulotomy* (release of contractures in the joint capsule by incision) are of value in cases in which the knee has subluxated. In Still's disease the age of the patient makes the conservation of the epiphyses imperative and the deformity is such that a trial of wedge casts demonstrates that further wedging will result in

complete dislocation. In this type of case operative correction of the subluxation is indicated. Often such deformity can only be partially corrected at the time of operation owing to contractions of the blood vessels and nerves. The correction is completed by means of wedge casts. Arthritic contractures of the *ankle joint* may require a tenotomy and posterior capsulotomy followed by wedging to correct the deformity.

Synovectomy, the operation of removal of the synovial membrane, is chiefly of use in the *knee joint*. In quiescent cases of arthritis of the knee which have stopped progressing under conservative treatment, synovectomy is of aid in those cases in which a chronic hypertrophic synovitis is the outstanding pathology. The joint space should be well preserved and a fair range of movement present. The quadriceps must not be greatly weakened and the patella movable. Any flexion deformity should be corrected by wedge casts before operation. Removal of the thickened synovia accomplishes the following:

1. Removal of an impediment to quadriceps action.
2. Relief of pain due to irritation of nerve endings in that portion of the synovia removed.
3. Possible removal of a focus of infection, as cases have been reported in which, following synovectomy, other involved joints have been improved.

Synovectomy is of most value in the case of *traumatic* etiology. The operation is of value in carefully selected cases of atrophic arthritis. Performed in atrophic cases which are active, the arthritic process may be aggravated so that the patient is more harmed than helped.

Resection of the patella is of value in cases of arthritis in which movement of the patella is limited and the chief source of pain. This is a development of the work of Brooke in removal of the patella in the treatment of fractures of this bone. This operation may be combined with other operations as synovectomy. Removal of the patella, which is fixed, allows better quadriceps action and, in selected cases, is of value. Here again, as in all surgery upon arthritic joints, the case that is *traumatic* in origin, as localized osteoarthritis following a fracture of the patella, is most suitable for this operation.

Chicilotomy (excision of osteophytes) is of value in some cases of hypertrophic arthritis in which the osteophytes form a definite block to movement. Pain may be lessened in cases in which the osteophyte is pinching the synovia at the extreme of motion. The range of motion is usually not much increased

by cheilotomy, but may be aided by cheilotomy supplemented with wedge casts.

Arthroplasty (surgical construction of a new joint) is of value in selected cases. Ankylosis of both hips, knees, or elbows require that an arthroplasty be done upon one joint. In bilateral ankylosis, it is advisable, especially in the weight-bearing joints, to leave one joint ankylosed for stability and perform an arthroplasty upon the more favorable joint to allow motion. Arthroplasties are satisfactory in the knee, hip and finger joints. The motion of the elbow can be restored by either excision of the joint or arthroplasty. In cases where only one weight-bearing joint is badly damaged, as a rule arthrodesis (surgically produced bony ankylosis) is most satisfactory. Arthrodesis results in a painless, stable extremity.

In hypertrophic arthritis of the hip joint, *malum coxae senilis*, the Smith-Petersen *acetabuloplasty* (resection of the anterior acetabular rim and joint capsule) is of value in relieving pain.

Arthrodesis (removal of the articular surfaces so that bony surfaces fuse together or, in the extra-articular operation, bridging the joint with a graft) is valuable in monarticular cases in which a stiff, painless joint is preferable to limited movement with pain. It is particularly useful in the weight-bearing joints where stability is more essential. Bilateral or adjacent joint involvement is a contraindication. The subastragalar joint, ankle, knee, hip, sacro-iliac, spine, shoulder and wrist are all well adapted to arthrodesis. Deformity is corrected at the time of operation by removal of suitable wedges of bone, the joint being fused in the position of maximum function for an ankylosed joint.

Osteotomy (surgical fracture of a bone and replacement of the fracture in a more favorable position) is of value in correcting cases of bony ankylosis in deformed position. Osteotomy through or below the intertrochanteric area of the hip is particularly useful. In some cases partial displacement medially of the distal fragment, so that when union occurs between the fragments a ledge is formed which bears weight through the lower acetabular rim and the shaft of the femur, aids greatly in relieving pain. This procedure is advocated by McMurray in cases of *malum coxae senilis*.

Conclusions.—In conclusion, the importance of *prevention* of deformity cannot be overemphasized. In atrophic arthritis, in conjunction with the indicated medical treatment, immobilization while the condition is acute and splinting to

prevent deformity will make the patient much more comfortable, allay the inflammation, aid in arresting the progress of the disease, and definitely prevent deformity. The corrective measures outlined are all of value in properly selected cases. Indeed, the case of deformity which cannot be helped is unusual.

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RECONSTRUCTIVE SURGERY IN CHRONIC RHEUMATOID
ARTHRITIS*

MANY patients presenting themselves at the Arthritic Clinic of the Abington Memorial Hospital fall in the group of those who, due to lack of proper supervision, have developed deformities which eventually lead to further damage of the involved joints and in some cases wheel-chair crippledom. In light of present knowledge of the treatment of arthritis, especially the chronic rheumatoid type, there is little excuse for the development of joint deformity when the case is seen in its early stages. Much of the deformity encountered in advanced stages can be prevented by simple measures, such as proper positions of bed rest, plaster shells and supervised exercises.

The care of rheumatoid cases is primarily a medical problem, but when certain deformities occur it is important that the responsibility of managing the patient's recovery be shared by an orthopedist. Contractures of joints may be sometimes entirely corrected by *plaster shells* (Fig. 202) and proper positions of rest in bed without the use of pillows. There are cases, however, in which deformity has progressed to the extent that reconstructive surgical measures to the joint should be utilized.

Orthopedic and surgical measures should be preceded by a thorough study of the arthritic patient, and an "equilibrium" should usually be established by means of bed rest.

Important groups of muscles may at times be developed to advantage by means of muscle-setting exercises in order to lay the groundwork for the planned corrective surgery.

* Acknowledgment is made to Dr. Ralph Pemberton for permission to use cases from his ward service in the Abington Memorial Hospital.

Indications for Operation.—The patient who has been confined to a wheel chair or bed for a period of years is a sociologic problem to his family and many times to the community. Often the disease has been "burned out" for years, the patient is free from pain and is perfectly comfortable in a bed or chair, but is still unable to walk or perhaps to feed himself. His disabilities are due to joint damage, which the healing processes of the body have been unable to repair. Such



Fig. 202.—Top—Complete shell; bottom—half shell.

cases call for sound judgment on the part of the surgeon because multiple joint involvement is the situation usually presenting. This being the case, several operations may be deemed necessary before the patient can become a useful individual. Such individuals *should not be operated upon* until the disease has been arrested for a period of six months to a year. The *sedimentation rate* should be within normal limits. These patients are always poor surgical risks because

they have been inactive for years. The individual patient should be permitted to decide whether or not he cares to take the risk of surgery or continue in his usual handicapped fashion. Many operative procedures may be employed but the one selected should be chosen on the basis of the pathologic changes in the affected joint and the appraisal of the patient as an operative risk.

It is very important that such involved joints be not completely immobilized and that, if surgery is resorted to, this measure be undertaken before the cartilage is destroyed.

SYNOVECTOMY

Hyperplasia of the synovial membrane is a common feature in chronic rheumatoid arthritis. Thickening and hypertrophy of the synovial membrane may persist even after the disease has become inactive and may be a cause of disability in the involved joints. This membrane may be thickened and thrown in folds, bringing about mechanical interference with normal joint function. A chronic effusion may be present and the scarred and thickened membrane may prevent normal drainage of the interchange of joint fluids.

If the knee is involved, tenderness will be evident in the region of the infrapatellar fat pad, with pain and restriction of motion upon attempt to completely extend the knee. x-Ray examination should be made to determine whether or not the pathology is chiefly confined to the soft tissue, and to ascertain the amount of damage that has occurred in the articular cartilage. When the usual supportive measures have been tried with unsatisfactory results and the persistent pathology is essentially confined to the synovialis, synovectomy may be resorted to. Synovectomy must be performed *cautiously*, and only in *selected* cases, by one experienced in this field. Without such selective precautions, this procedure may result in further limitation of joint motion and the occurrence of more pain and disability.

Technic.—A tourniquet is applied to the thigh to facilitate dissection. The knee joint is opened by an internal peripatellar incision, which extends from the uppermost limit of the joint cavity to the anterior tibial tubercle. Contents of the joint are evacuated and the dissection of the synovial membrane begun from above downwards. Separation of the thickened synovia is easy in the upper portion, the so-called bursa of the knee. The lateral recesses are more difficult to clear completely of the inflamed membrane, but persistence

with knife and scissors will enable this to be done. Often pannus will be found extending over the cartilaginous surfaces and this should be scraped away. If the patellar surface is greatly eroded, the entire patella may be removed to avoid subsequent traumatic arthritis, and it is usually best to remove the infrapatellar fat pad. At times an extension into the popliteal space may be present, the so-called Baker's cyst. This should be removed entirely by posterior incision as it will be found that the lining membrane and contents are similar to that of the joint itself.

After the dissection is completed, the tourniquet should be loosened and any active bleeders coagulated. It is not necessary to stop all oozing. The incision through the muscle and ligamentary layers is then closed by a running suture of chromic catgut and the skin by a lock stitch of the same material. Voluminous pressure dressing is then applied to the knee and a posterior molded splint from fold of the buttock down to the Achilles tendon. This splint is kept in place for a week, during the early period of the healing of the wound itself, and is then removed to permit early active motion. Much depends on the patient beginning to move the knee as early as possible to prevent formation of adhesions. Some patients will fail to cooperate and it will be necessary in two or three weeks to flex the knees forcibly under pentothal sodium or gas anesthesia to break up the early adhesions before they consolidate. In this period physiotherapy in the form of baking and massage will do much to shorten the convalescent period and improve the muscle tone. Weight-bearing may begin in from two to six weeks. No patient in this series has failed to get less than 90-degree flexion and in some the range of motion is entirely normal.

The following case illustrates indications for the aforementioned procedure:

Case I.—Mr. J. P., aged fifty-three, was admitted to the Arthritic Clinic suffering from chronic rheumatoid arthritis of eight years' duration, involving the knees, hands, shoulders and ankles. A thorough medical checkup revealed secondary anemia (Class III), gingivitis, chronic prostatitis and intestinal stasis. The patient was placed in bed on a balanced medical program for six months. At the end of this time the arthritis had subsided in his hands, shoulders and ankles, but he was still unable to walk without fulness in the knees and recurrence of pain. x-Ray examination of the knees showed little damage to cartilage but marked thickening in the soft parts. Bilateral synovectomy was performed under spinal anesthesia.

Results.—This patient has been ambulatory for nineteen months since the operation, with complete range of motion in both knees; no pain or discom-

fort is present in the knees, and some difficulty with the right ankle has been cared for with proper shoes.



Fig. 203.—A, Showing some evidence of chronic pulmonary osteoarthropathy. B, Knee before synovectomy.

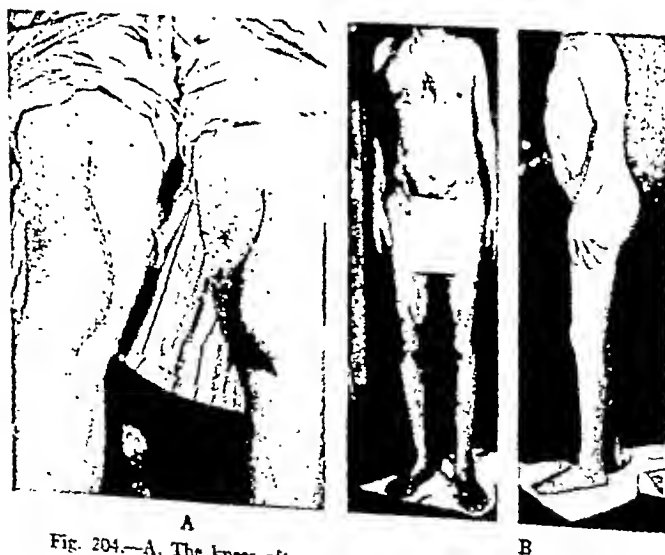


Fig. 204.—A, The knees after synovectomy. B, Patient standing.

In the following case the results were not as favorable:

Case II.—Mrs. V. C., aged forty-two, had chronic atrophic arthritis for one year and seven months, with generalized involvement of hands, shoulders,

jaws, elbows, knees and ankles. She came to the Arthritic Clinic in a wheel chair six months after onset. Studies revealed Type IV gingivitis with infected teeth; diseased tonsils; anemia, and endocervicitis, with possible malignancy (which was later ruled out by means of a cervical biopsy); marked malnutrition, gastro-intestinal dysfunction with constipation; knees distended with fluid, and great pain when standing. x-Ray of knees showed no cartilage damage. The patient was in the medical ward for ten months, during which time the above factors were cared for and several transfusions were given. Preliminary muscle training exercises over a period of two to three months were followed by bilateral synovectomy on both knees under spinal anesthesia.

Results.—Quadriceps femora were developed so that patient could completely extend both legs without any subluxation of the knees. After discharge the patient could not return to hospital for proper supervision. Her husband lost his position and the patient refused to eat; she could not sleep because of worry. She returned to the hospital for six months following flareup of arthritis with swelling of right knee. Attack subsided and patient is now home, fourteen months after the operation, under supervision of family doctor; she is able to walk and the arthritis is arrested.

CAPSULOPLASTY

Constant flexion of the knees to the extent of 20 to 30 degrees usually leads to life in a wheel-chair. There is not only contraction of the capsule in such joints, but also marked wasting and contracture of muscle structures, iliotibial band and biceps tendon. The knee should be examined by x-ray for evidence of damage to cartilage. When little damage is present, posterior capsuloplasty may be considered. The end result of such procedures should be complete extension of the part with its normal range of motion.

Technic of Posterior Capsuloplasty.—The skin preparation is started the day before the operation. Anesthesia as indicated, usually spinal. Tourniquet applied to the thigh. Incision 12 to 15 cm. in length over the lateral side of the knee. Iliotibial band and biceps tendon exposed. The iliotibial band cut transversely, approximately 2 inches above the joint interval. The external popliteal nerve is identified and retracted from the operative field. The biceps tendon is freed from the point of insertion upward 4 or 5 inches. The tendon is split for a distance of about 2 inches and the two portions divided at different levels and turned back, leaving them in a manner in which the two ends are later united effecting a tendon lengthening of about 2 inches. Incision made through the capsule at this point, opening the posterior compartment of the joint. Capsule stripped upward from the posterior surface of the femur. Outer head of the gastrocnemius separated and subperiosteal dissection continued several inches upward above the knee joint and toward the midline of the femur.

Incision over the medial aspect of the knee from the adductor tubercle on the medial condyle to slightly below the joint line. Capsule opened and posterior capsule entered. Subperiosteal stripping of the capsule as on the opposite side to a point continuous with the dissection previously made. Gauze passed through the wound posteriorly to the femur to serve as a retractor. Knee acutely flexed viewing the posterior capsular space wide open. Knee is then straightened by gentle manipulation, resulting in stretching the soft parts and breaking whatever adhesions might be within the joint. Tourniquet is now removed, bleeding controlled. Wounds closed, ends of



Fig. 205.—Left knee after capsuloplasty. Right knee before capsuloplasty.

the biceps tendon approximated as above mentioned. Knee is fixed in extended position by the application of plaster cast from the toes to the groin. This cast is bivalved immediately. This is substantially the operation developed by Wilson.

Synovectomy and Posterior Capsuloplasty.—It is sometimes necessary to perform a synovectomy and a posterior capsuloplasty on the same joint in order to restore proper function to that joint. The following case will illustrate:

Case III.—Mrs. F. G., aged fifty-five, had arthritis for eight years. Prior to her admission to the Arthritic Clinic, the teeth and tonsils were removed and a hysterectomy had been performed. She presented marked clinical activity, with deformity of the fingers, restriction of motion in shoulders and marked swelling and pain in the knees, with a resulting flexion deformity of 30 degrees in the left and 20 degrees in the right knee. She presented marked secondary anemia. The patient was put on a conservative medical program

for two years. The hands and shoulders became quiescent. Despite the use of plaster shells she was unable to fully extend the knees or to walk without marked pain and swelling in the knees.

In such cases, with marked contraction of the joint capsule, capsuloplasty is indicated. Posterior capsuloplasty was therefore performed on the left knee and, six months later, synovectomy was performed on the left knee and a capsuloplasty was done to the right knee.

Results.—At present, six months following the last operation, the patient is able to walk without the use of crutches; has complete range of motion in both knees and much of the swelling in the right synovialis has disappeared; still has some slight pain upon pressure in the right infrapatellar region.

In the following case the results were unfavorable:

Case IV.—J. M., aged thirty-three, had acute atrophic arthritis for eight years with active involvement of the hands and hips and swelling of the right



Fig. 206.—Case IV. Before capsuloplasty.

knee, with a permanent knee flexion of 135 and motion of 45 degrees. Medical studies revealed two infected teeth (with Type II gingivitis), diseased tonsil stumps, chronic prostatitis and some dysfunction of the gastro-intestinal tract. The above factors were properly cared for over a period of fourteen months. The sedimentation rate was 10 mm. in one hour at the time of the right capsuloplasty, and the arthritis in the hands, hips and right knee was considered to be quiescent; but the permanent flexion of the right knee remained and the patient was forced to use a cane. A right capsuloplasty was performed under spinal anesthesia in the usual manner. Four days following the operative procedure the patient developed surgical erysipelas. Numerous transfusions, sulfanilamide, erysipelas serum and x-ray treatments were used to no avail. Death occurred nine days after the operation as a result of the development of acute parenchymatous nephritis. Five days following the surgical erysipelas, cultures were taken from the operative field and were found to be negative for the erysipelas organism, and cultures from the surgical field were found to be negative upon autopsy.

NEED FOR PROPER FOLLOW-UP SYSTEM

It is most important that a careful follow-up system be established so that any subsequent arthritic activity may be seen early and controlled. The psychologic effect on a patient enabled to walk by an operation after being bedridden for months is marked and may act as a stimulus for further betterment. The increase in activity made possible by the correction of the disability encourages the patient to persist in a regimen enabling him to reach a higher level of general health.

SUMMARY

1. All patients should be thoroughly studied and essential medical measures carried out *before* resorting to surgery. ✓

2. Conservative measures, such as splinting, corrective and muscle-setting exercises, should be utilized prior to surgery.

3. Synovectomy or capsuloplasty are indicated only after conservative measures have failed to bring about complete restoration of joint function.

4. Synovectomy and posterior capsuloplasty, together with other selected surgical measures, are of great importance in the reconstructive program of patients crippled by the end results of arthritis.

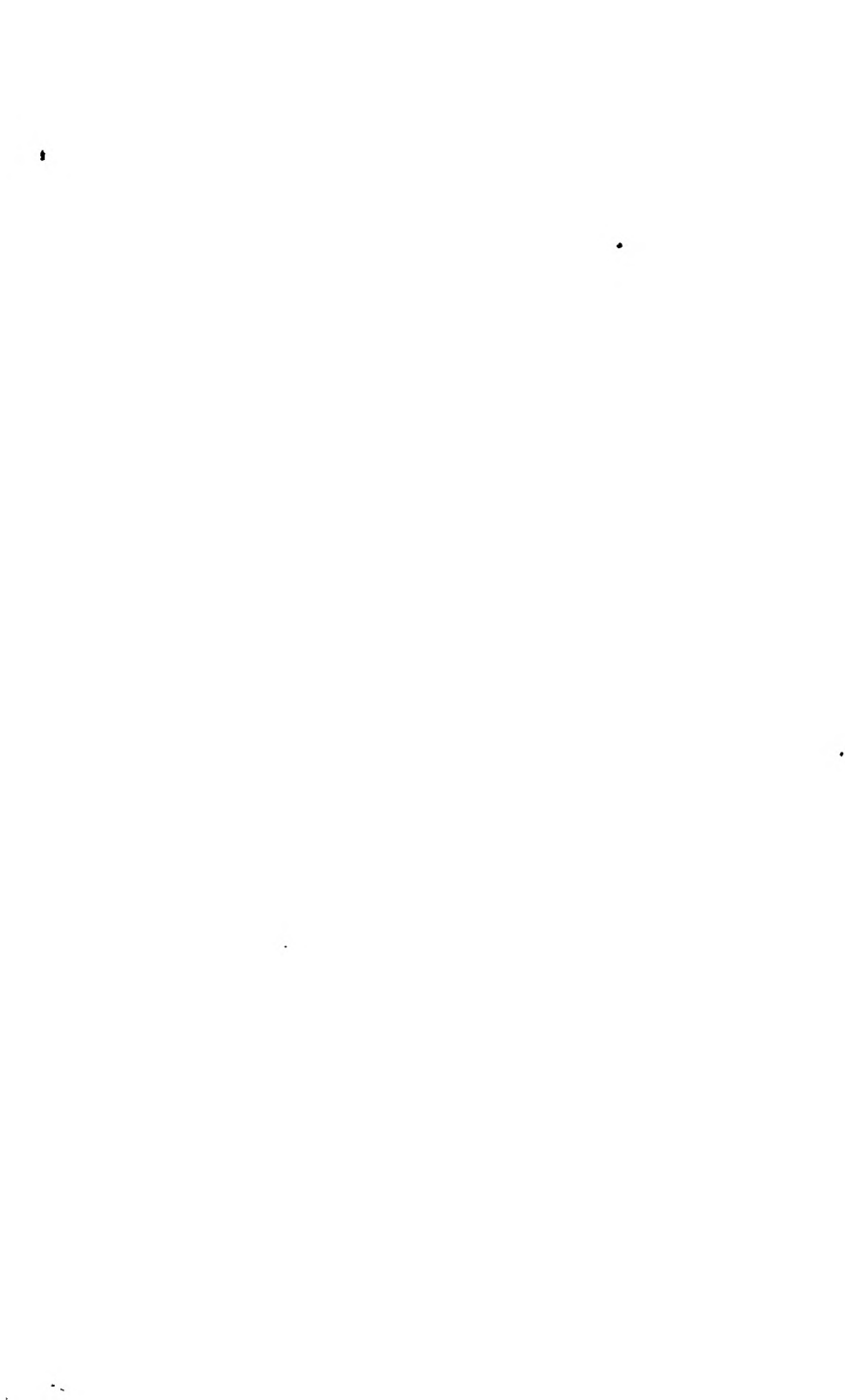
5. Critical surgical judgment must be exercised in the selection of the specific measure to be utilized to fit the presenting pathology and deformity found in the involved joints.

6. Surgery is contraindicated while active arthritis is present in the involved joint.

7. Successful results are obtained only by close cooperation of the surgeon and internist.

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THE DIAGNOSIS AND TREATMENT OF LOW BACK PAIN

THE subject of low back pain is rather complicated by reason of the fact that pathologic change in any of the structures in the lower part of the back—*bones, joints, ligaments, muscles, or nerves*—may be the cause, either singly or in combination, of pain in this region. Many cases present *multiple* causes.

It is the purpose of this paper to try to outline the present status of low back pain. There have been recent advances in the past few years which have done much to clarify this difficult subject. The diagnostic use of *novocaine*, as developed by Steindler, is of definite aid. *Novocaine* as a therapeutic agent, as advocated by Leriche, helps some patients surprisingly. The work of Freiberg on spasm of the piriformis muscle, of Ober on the contractures of the iliotibial band and abductor fasciae, and of Heyman on strain and contractures of the gluteus maximus, have helped to clarify the causes and added methods of treatment. Herniation of the nucleus pulposus and hypertrophic scars of the ligamenta flava are now well established causes of some cases of the sciatic syndrome.

Why Is the Lower Part of the Back So Susceptible to Strain?—Several reasons may be cited in answer to this question.

The assumption of the *upright posture* by man, with resulting acute angulation between the sacrum and the lumbar spine, is generally cited as a predisposing cause. The frequency of *anatomic anomalies* in this area is obvious in any series of x-rays of this area. The fact that two long *levers*, either the entire spine or the lower extremity, may exert severe forces upon the low back is also evident. Perhaps the commonest cause is the insufficiency of the low back musculature in modern man. *Sedentary occupations*, or manual occupations in which the worker remains seated all day, together with poor

habits of posture, result in a back which is barely compensating. A *strain* of lifting or a fall, an excessive increase in weight or even increased weight-bearing, will increase the load so that the symptoms of strain or more serious injury result. An *illness* resulting in further loss of muscle power may be the cause of insufficiency of the muscles and strain. In the back subjected to continued mild strain, *chronic irritation* increases the changes which appear as osteoarthritis in later life.

A knowledge of the *anatomy* of the lower part of the back is *essential* to an understanding of this subject. As the length of this article is limited, the reader is advised to refer to a standard text, or better, to an atlas of anatomy.

DIAGNOSTIC PROCEDURES

Diagnostic Use of Novocaine.—The diagnostic use of novocaine, as described by Steindler, has demonstrated that in many cases of low back pain with sciatic radiation the sciatic pain is referred from an *irritated focus* in the low back. The starting point, referred to as a "trigger point" by Steindler, is the point of origin of a reflex passing over the posterior primary division of the spinal nerve and the sciatic pain is a referred pain. In the use of this test the following points must be satisfied:

1. Irritation of the trigger point by the hypodermic needle aggravates the local and sciatic pain.
2. Injection of this point with 1 per cent novocaine relieves the local and the sciatic pain.
3. The leg signs becomes negative.

Steindler's "*trigger points*" are listed as follows, according to the structure suffering strain:

1. *Sacrospinalis syndrome*, medial to posterior superior or inferior iliac spines.
2. *Lumbosacral syndrome*, over lumbosacral junction between spinous processes of the fifth lumbar and the first sacral vertebrae.
3. *Gluteal syndrome*, over the origin of the gluteus maximus just lateral to the most posterior iliac crest.
4. *Transversosacral syndrome*, at the anomalous articulation of the sacralized transverse process.
5. *Tensor fasciae latae syndrome*, at the lateral border of the iliotibial band, usually accompanied by a positive Ober's sign.
6. *Myofascial syndrome*, vague tenderness along the sacrospinalis muscle and its fascial sheath.

Ober's Test and Other Procedures.—The work of Heyman, Ober, Freiberg and others demonstrates another mechanism of sciatic pain. Ober described a sciatic syndrome in

which the *abductor* or *lateral hip fasciae* are contracted and the sciatica is relieved by *surgical release* of the contracture. The patient is tender over the posterior portion of the iliotibial band. The contracture is best demonstrated by Ober's test:

The patient lies upon the sound side grasping the underneath flexed knee with both hands, thus holding the underneath hip in full flexion. The upper or involved thigh is relaxed and, with the knee flexed to a right angle, is lifted into a position of moderate abduction, the thigh being kept in the coronal plane. Although relaxed, the thigh remains in abduction in cases with contractures. In the *normal* case, the knee can touch the examining table.

Freiberg, in cases of sciatic syndrome with tenderness over the insertion of the piriformis muscle and limitation of straight leg raising, has secured relief by *sectioning* the tendon of the piriformis muscle. Others have used *novocaine injections of the piriformis* and secured relief. Heyman's procedure of *subperiosteal stripping* of the area of the posterior superior iliac spine produces relaxation of a portion of the gluteus maximus. This procedure may be used in cases not yielding to conservative measures in which there is definite tenderness and pain of the origin of the gluteus maximus and a positive Steindler's test.

The above procedures of Ober, Freiberg, Heyman, and the use of novocaine and the strapping of the sacro-iliacs with adhesive tape, have all one common point: *relaxation of the gluteal musculature*. It is well to remember, however, that patients relieved by such measures are not cured. Further treatment to correct postural defect, improve the musculature and restore and preserve full range of motion is essential.

The above investigators have established another mechanism of sciatica: *spasm or contracture of the gluteal or underlying musculature*. This spasm may be due to fatigue, myofascitis, or irritative lesions, either mechanical or inflammatory, of the sacro-iliac joint or its ligaments to which a large portion of the gluteal musculature is attached.

General Physical Examination.—The clinical examination of a patient with low back pain must be thorough. The *history* should be investigated for the following points: Trauma, either acute or chronic, is common in some occupations. Trauma, applied through the spinal lever, usually affects the lower lumbar and lumbosacral areas, while when applied through the extremity lever, the sacro-iliac area is affected. Inquiry should be made regarding *duration* of previous attacks.

The *site of pain*, and the type, constancy and radiation are all important. The relation to exercise and rest is noted. Arthritic patients usually have some involvement in *other areas*. *Stiffness* on arising, *aggravation* by changes of weather, and involvement of a considerable section of the spine are also suggestive of arthritis. Low back pain may be a symptom in *genito-urinary*, *gynecologic* and *neurologic* conditions; hence these systems should be investigated. The *colon* may refer pain to the back. Indeed, the body as a whole must be considered, as general *disorders of nutrition* or *anemia* may cause muscular insufficiency sufficient to cause back strain. *Neurasthenia* should be watched for and, if present, treated. Symptoms suggesting *focal infection* in the various systems are queried. *Foot fatigue* is usually present in postural cases.

Examination of the Back.—The physical examination should be of the entire body. The essential points in examination for low back pain follow:

Posture is important, as any postural defect must be corrected. The following defects are very common and are a cause of strain: *Flat feet*, either of the anterior or main arches, or both; *inequality* in the *length* of the extremities; *lumbar lordosis*, or loss of the normal lumbar curve; *relaxation of the belly wall*; and the presence of a lateral curvature or *scoliosis*.

The *range of active motion* of the spine should be noted, both standing and sitting. In strain of the sacro-iliac areas, the range of motion is improved with the patient sitting while limitation of lumbar movement is unchanged. Movements producing pain and at the angle at which pain occurs are noted.

The *gait* of the patient, his *freedom of movement* in getting down and up from a chair, in climbing on and off an examining table, and in dressing and undressing, should be noted, particularly in the traumatic case complicated by litigation. During the above acts the patient, if malingering, may forget to act his part.

Palpation of the back is done with the patient lying upon the examining table. Tenderness or muscle spasm is noted. Palpation must be thoroughly done, investigating especially the spines and interspinous ligaments, and sacro-iliac, lumbosacral and coccygeal areas. The course of the spinal nerves along the outer border of the sacrospinalis musculature is carefully palpated. Rectal palpation notes tenderness or other palpable abnormality of the coccyx, sacrum, sacrococcygeal joint, sacro-iliac joints and sacrotuberous ligaments. The usual abdominal examination is done.

The lower extremities are examined, the *range of motion in hips, knees and feet* and the *reflexes* being noted. If there is referred sciatic pain, sensation should be noted also. Back strain may be due to restricted movement of the hip or muscle weakness.

SPECIAL TESTS.—In examination of the low back many special tests are used, a brief description of which follows:

Goldthwaites' sign consists of straight leg raising. The patient lies upon his back and the thigh is flexed to 90°, the knee being fully extended. This sign is also spoken of as *Lasègue's sign*. Lasègue described flexion of the hip to 90° after which the knee was extended. In straight leg raising the following structures are put under tension: The sciatic nerve, which in cases with the sciatic syndrome causes pain in the first part of straight leg raising. As the hip is flexed the hamstring and then the gluteal muscles are tensed. Further flexion results in pull through the hamstrings via their origin on the ischial tuberosity and the sacrotuberous ligaments upon the posterior long sacro-iliac ligaments and joint capsule. The last part of flexion rotates the ilium and exerts a shearing strain on the sacro-iliac joint. The lumbosacral area is little affected by this test save in extreme flexion.

Gacnslen's sign involves a similar mechanism save that the ilium is rotated in the opposite direction. The thigh and the knee are flexed against the abdomen and the opposite hip is hyperextended. This maneuver is useful, as the sciatic nerve is not stretched.

Laguere's sign is also of use. The patient lies upon his back, the knee is flexed and the hip flexed and abducted. The examiner then presses down upon the opposite anterior superior iliac spine and on the knee. The adductors of the hip are put under tension, and the iliac portion of the sacro-iliac joint is forced against the sacral surface. This sign is of value in that the joint is put under strain without pulling upon the sciatic nerve and gluteal structures.

Compression of the iliac crests produces pressure upon the sacro-iliac joints without disturbing the lumbosacral.

One-leg standing also throws strain upon the sacro-iliac areas.

Ober's sign has been described in the discussion of mechanisms for the production of sciatica.

The lumbosacral and lumbar areas can be examined by means of *passive movement* without straining the sacro-iliac areas by the following method: The patient lies upon the back,

both hips and knees flexed acutely; with the examiner grasping the ankles with one hand and the knees with the other, the lumbar spine can be put through all movements save extension.

In very *acute* cases, full examination may be impossible and an accurate diagnosis cannot be made until the condition subsides somewhat. Rest in a fracture bed with bilateral Buck's extension, heat and analgesics usually relieve the condition in a few days so that a more accurate diagnosis can be made.

The diagnostic use of *novocaine* has been outlined above. This procedure is of definite diagnostic value and should be used in most cases of strain.

Radiographic Examination.—The *x*-ray is an essential aid. Many bone lesions, such as fractures, neoplasms, both primary and secondary, neurotrophic lesions (Charcot), dislocations, osteomyelitis, tuberculosis, congenital anomalies, ankylosing spondylitis and osteoarthritis, present very characteristic *x*-ray appearances. The sacro-iliac areas should be *x*-rayed stereoscopically. The lumbosacral and lumbar areas are usually best shown in anteroposterior and lateral views, and the articular facets of the lumbosacral area in oblique views. The lumbosacral angle should be noted, for, when increased, it suggests postural strain. Cases of strain usually show no other positive *x*-ray findings. Condensation of bone along the sacro-iliac joints suggests arthritis. A decrease in the height of an intervertebral disk is suggestive of a displacement of the nucleus pulposus.

Diagnosis of displacement of the nucleus pulposus or hypertrophic scar of the ligamenta flava is made by *myelograms*. Four or 5 cc. of *lipiodol* are injected into the subarachnoid space through the second or third lumbar interspace. The patient is immediately examined fluoroscopically. Tilting the table causes the lipiodol to flow up and down the subarachnoid space. Any obstruction is noted and *x*-ray plates are taken. Filling defects at the level of the intervertebral spaces indicate herniation of the nucleus or an enlarged *ligamentum flavum*. The use of lipiodol is not to be undertaken lightly, as at least a temporary leptomeningitis results. Cases of more serious injury have been reported. The author believes that Watson-Jones states the proper procedure to be followed in the following: "*If routine radiographic and clinical examinations have excluded other causes, if the case has resisted conservative treatment for more than six months, and if the symptoms have recurred after temporary relief of three months' immobilization*

in plaster, *lipiodol injection is justified.*" In short, if thorough conservative treatment fails then lipiodol is justified.

The blood Wassermann, *sedimentation rate*, complete blood count, *urine analysis* and *spinal fluid examination* are necessary in many cases. An increased sedimentation rate in the absence of anemia or an infectious focus is suggestive of arthritis. The spinal fluid examination should note pressure, colloidal gold curve and protein content, and should include the Queckenstedt test, cell count and Wassermann test. A spinal fluid protein of over 50 mg. is suggestive of a disk or ligament lesion. Instances of these lesions have been reported in which a block was present.

DISTINGUISHING FEATURES OF LOW BACK LESIONS

The remainder of this article will deal briefly with diagnostic points of value in low back *strain*, lesions of the *intervertebral disk* and *ligamenta flava* and *arthritic affections* of the low back. It is to be emphasized again that many cases present combinations of the above, and the diagnosis must be made to fit the findings in the specific case, rather than making the case fit a diagnosis. One must evaluate all the possible factors in order to direct treatment to the correction of each factor. The goal should not be a symptom-free patient in a brace but rather a symptom-free patient pursuing normal activity *without* a brace.

Strain of the Lower Back.—Low back strain may be due to *postural errors* or *trauma*. Often the patient with postural defects of flat feet, lumbar lordosis, sagging abdomen and obesity is symptom-free until some trauma is literally the last straw on the camel's back. In any case of low back pain with postural error, the postural error must be corrected as part of the treatment. Severe cases of postural strain may present secondary pathology such as contracture or the sciatic syndrome.

Fascial contractures occur in neglected or severe cases. These cases frequently do not yield to conservative treatment and, if Ober's sign is positive, Ober's operation for the release of contractures in the iliotibial band, fasciae latae and hip abductor intermuscular septa should be done. Heyman's operation of subperiosteal stripping of the posterior superior iliac spine should be done in resistant cases in which clinical findings and Steindler's test indicate the symptoms as originating in strain in this area.

Strains of the sacro-iliac and lumbosacral areas are differentiated by Smith-Petersen in Table 1.

TABLE 1
DIFFERENTIATION OF LUMBOSACRAL AND SACRO-ILIAC STRAIN

	Lumbosacral.	Sacro-iliac.
History of trauma.....	Leverage from above with spine in flexion.	Leverage—unilateral via lower limb.
Pain:		
1. Referred to	Fifth lumbar area. First sacral area.	Fourth and fifth lumbar vertebrae. First and second sacral vertebrae.
2. Distribution.....	Lateral side of leg, dorsum of foot, sole of foot.	Posterior aspect of thigh. Adductor regions.
Points of tenderness.....	Iliolumbar ligaments, spinous processes, fourth and fifth lumbar, first sacral vertebrae.	Inferior sacro-iliac ligaments. Greater sciatic notch.
Movement of spine:		
1. Standing.....	All lumbosacral movements are restricted.	All free save unilateral side bending, <i>forward</i> bending in extreme range.
2. Sitting.....	All lumbosacral movements are restricted.	Forward bending free.
3. Lying.....	All lumbosacral movements are restricted.	Free.
Special tests:		
1. Straight leg raising..	Limited in extremes, both sides equally.	Unilateral limitation at small range.
2. Compression of pelvis	Nil.	Occasional pain in sacro-iliac joint.

Traumatic injuries to the joints usually present injuries of the above types plus deep tenderness over the interarticular, lumbosacral or sacro-iliac joints. Novocaine injection may confirm the diagnosis. These cases are more resistant to treatment.

Lesions of the Intervertebral Disk and Ligamenta Flava.—Intervertebral disk and ligamenta flava injuries, with subsequent pressure upon the nerve roots, may be suspected when, following trauma, the first symptom is sciatica. An altered ankle jerk is common. The x-rays may show a decrease in the height of an intervertebral disk. The spinal fluid protein is above 50 mg. It is to be emphasized that diagnosis

depends on lipiodol myelography which should not be undertaken until conservative treatment has been thoroughly tried. Treatment consists of laminectomy and removal of the herniated nucleus pulposus or excision of the enlarged ligamenta flava.

Arthritic Affections.—The arthritic affections of the lower back are characterized by exacerbations without trauma, involvement of other joints, more widespread involvement of the spine and an increased sedimentation rate, save in the osteoarthritic cases. Fibromyositis, spondylitis deformans and osteoarthritis will be briefly discussed. Most of what has been said above regarding clinical localization of the areas involved is of value in these cases.

Fibromyositis is an affection of the muscle sheaths, tendons and fasciae. The chief disability complained of is inability to straighten the back after flexion. Careful palpation usually reveals tender nodules of fibrous tissue.

Spondylitis deformans (spondylitis ankylopoetica) is characterized by gradual involvement of the entire spine. These cases are very susceptible to any trauma. The x-rays show progressive ligamentous calcification in the later cases; in early cases condensation along the sacro-iliacs may be the only x-ray finding.

Osteoarthritis is also characterized by a generalized involvement. Many patients who show marked osteophytic formation on the vertebral bodies complain of little or no symptoms. These cases are very susceptible to trauma and are resistant to treatment.

TREATMENT OF LOW BACK PAIN

Treatment of the low back case requires that all possible factors be corrected. The general condition of the patient is considered and any defect which may lead to muscular weakness should be corrected. *Secondary anemia, neurasthenia* and *facal infection*, if present, should be vigorously combatted.

Obesity is a common cause of chronic strain and, if present, requires a reduction in weight. The cases which present spondylitis deformans (spondylitis ankylopoetica), rheumatoid arthritis and fibromyositis require the general measures dealt with elsewhere in this symposium.

Rest.—Rest of the injured or inflamed area is essential. In the mild case of strain, *adhesive strapping* may be sufficient, while the severe case with marked muscle spasm requires rest upon a *fracture bed* with bilateral Buck's extension until the

muscle spasm disappears. Regarding *casts* and *braces*, injuries of the lumbar spine require that the support extend from the mid-dorsal area to the buttocks. The sacro-iliac area requires support in the shape of a *belt* which compresses the sacro-iliac joints. Sufficient rest should be given to relieve the symptoms. In postural cases *corsets* are often of value to relieve the drag of a sagging belly wall. Flat feet should be supported by corrective shoes and arch supports. Inequality of the extremities is equalized by the use of *lifts* on the short extremity. Rest in one of the above forms is necessary until the patient can go without the support in comfort. Often one progresses from fracture bed with traction, to cast, to brace, to corset. In the arthritic cases, support must be given for a long time. Spondylitis ankylopoetica usually progresses to an ankylosed spine; the patient requires support in a long body cast or celluloid packet until the spine is ankylosed, in order to prevent severe flexion deformity.

Physical Therapy.—Such therapy is of value. If used too vigorously in the early stages increased reaction of the tissues may result, thus retarding recovery. Heat and massage are of value as the acuteness subsides, especially in fibromyositis. In chronic cases the massage should be as deep and forceful as can be done without pain. As the severe case improves, muscle setting should be used.

Muscle setting consists of contracting the muscle without moving the part. This is followed by *active exercises*. In the arthritic case active exercises must be used cautiously. During the acute stages active exercises are contraindicated. In quiescent arthritis, traumatic back injuries and the postural case, active exercises are of great value. Many patients who wear braces can build up their own musculature by exercises and discard the braces. The exercises should be designed to increase the power and assure a full range of movement in the hips, sacro-iliacs and lumbar spine.

Manipulation of the sacro-iliac joints aids some cases in which periarticular adhesions or hamstring contractures are present. It is usually contraindicated in the arthritic case. Active arthritis is an absolute contraindication. Manipulation, to be successful, should be done with the patient well relaxed by anesthesia. The joint is manipulated by means of straight leg raising and extension while the opposite thigh is flexed. As in all manipulation, the object is to restore a full range of mobility to the part. In the sacro-iliac joint the extra-articular structures are affected more than the joint proper. Manipula-

tion should be done once in each movement, as pumping merely traumatizes and increases the postmanipulative reaction. Manipulation is dangerous if abused, as peroneal palsy or fracture of the neck of the femur may occur. In the lumbar area manipulation is not of much value and there is the danger of aggravating a lesion of the intervertebral disk or ligamenta flava. In any case treated by manipulation the gains in range of motion must be preserved by active exercises as soon as the reaction, secondary to the manipulation, subsides.

Novocaine Injections.—The use of novocaine by repeated injections is of definite value in many cases of strain and spasm. Leriche believes that the injured tissues through a reflex arc stimulate the blood vessels in the same area to dilate. Vaso-dilation increases effusions and a vicious cycle is set up. Novocaine injections in cases of strain are repeated every five days if successful. In cases of sciatica with pyriformis spasm, novocaine injected into the pyriformis and about the sciatic nerve has given definite relief. Our experience has been that many cases require about 100 cc. of 1 per cent novocaine to give relief; this dosage, of course, not only affects the pyriformis but relaxes a great deal of the gluteal musculature. Novocaine is of definite aid both diagnostically and therapeutically.

Treatment of Contractures.—Contractures are present in most persistent cases of strain or arthritis. Contractures, most commonly in the hamstrings or hip abductor fasciae, throw an additional mechanical strain on the sacro-iliac or lumbosacral areas. The limitation of movement in the hip requires that the adjacent joints move through a greater range of motion to compensate. Mild to moderate cases may be stretched by *active exercises*. *Manipulation* has a place in stretching the hamstring contractures. *Ober's operation* of releasing the abductor fasciae and iliotibial band, and *Heyman's procedure* of subperiosteal stripping of the posterior superior spine are of value in these cases. It must be remembered that these operations correct a contracture and nothing more. Operation must be followed up by measures to correct the underlying condition. Of these measures, exercises are probably the most important.

Arthrodesis of the lumbosacral junction or the sacro-iliac joint is of value in cases of strain in these areas not relieved by the above. Lesions of the intervertebral disk and ligamenta flava must be excluded before arthrodesis.

Herniation of the nucleus pulposus or hypertrophic scar of

the ligamenta flava require *laminectomy* in most cases. The laminectomy should be repaired by a fusion produced by osteoperiosteal grafts reinforced with the removed bone of the spinous processes and laminae.

"No problem has been more perplexing than the low back pain of orthopedics, but with increased knowledge and after an immense amount of research, order and hope have evolved from chaos."—*Walter Mercer*.

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INTEGRATION AND COORDINATION OF THERAPY IN THE CARE OF ARTHRITIS

THE consensus of students everywhere is that arthritis is a disease of systemic nature with joint manifestations.¹ At least two great types constitute the syndrome, and while the final etiology of these types is by no means established, the evidence is quite clear that it is in any event varied. In view of this generic nature and varied etiology it is almost axiomatic that therapy must be directed at many factors and cannot depend upon any *single* agency.

The papers which constitute the present symposium reflect the rapidly changing conception entertained toward the etiology of the arthritides. For many years the striking manifestations in the joints confined attention to those regions and it was considered that the joints alone were importantly involved. By the same token, the limitations inherent in the doctrine of focal infection, which so long dominated this field, were appreciated by a few students, including the writer, twenty-five years ago by virtue of their interest in the disturbances of physiology which accompany the disease, but to utter a heresy based on such an outlook was then almost anathema. Focal infection can now be seen in a proper perspective, however, as one of a number of factors, such as physical fatigue, exposure, nervous strain, faulty nutrition, trauma, etc., which may act as "precipitating" factors and set in motion a train of events which constitute the syndrome. It is certainly not possible today to state with finality the several links of the chain so forged. A host of considerations, however, many of which are presented in the present volume, necessitates the hypothesis that the above precipitating factors operate to make demands upon some of the "*master tissues*" of the body, especially the pituitary and, through these, upon the chain of endocrinous and

hormonal influences which condition growth, the metabolism of bone, blood flow, the water balance and the activities of the sympathetic nervous system. At all events, only an outlook which has room to contemplate the varied expressions of the syndrome in some such way can be expected to give these adequate therapeutic consideration.

Need for Integration and Coordination of Therapy.—It follows, therefore, that if therapy is to proceed along many lines, it must be integrated and coordinated; that is, *welded into a whole*. Almost all therapy of known efficiency in medicine carries with it both limitations and dangers. Perhaps in no other syndrome is the truth of this more obvious than in the field of rheumatoid disease. In view of the fact that many systems of the body are involved, it becomes tempting to the increasing number of those who appreciate the widespread nature of the problem, to bring to bear as early and as vigorously as possible the several agencies which are known or believed to be of benefit. It is precisely here, however, that *great caution* must be exercised. The arthritic is at best a fragile subject, as has been too often demonstrated on the operating table. Unless adequate appreciation is entertained of the *instability of the nervous system*, the changes in the blood and in the finer vascular beds, the disturbance of metabolism in the fluid tissues, as well as in the muscular and tendinous systems, all attempts at integration of therapy or, indeed, at any line of therapy vigorously pursued, are likely to result in a medical debacle.

The extent to which arthritics, already reduced to a low level by the chronicity and suffering of their invalidism, have been subjected to operative procedures, vigorous forms of physical therapy, the injection of vaccines, of nonspecific protein, and the application of such measures as hyperpyrexia, is a commentary upon the unfamiliarity of many of the profession with the problem as a whole. A valuable leaf could be taken from the book of genito-urinary surgeons whose practice, in prostatectomy among the aged, is to establish an equilibrium of the individual as a whole before any radicalism is attempted. The sick arthritic is in precisely the same state, or worse, as that experienced by the aged surgical subjects above referred to. It should appear reasonable, therefore, to all who are required to treat arthritics, to provide at the outset that *nothing be done to disturb further the precarious equilibrium*, such as it is, that already exists; at least until the steps under consideration are shown to be essential. If the above

general premises be accepted, and nearly all well considered opinions support this view, it follows that integration and co-ordination of treatment in the arthritic become almost a phase of therapy in itself.

Preventive Measures.—By the same token that the dislocated systems of the body can be adjusted more or less successfully to or toward a normal equilibrium, so can *minor disturbances* in those systems be influenced in the prodromal stages of the disease. This means that much can be accomplished in the way of preventive medicine in the field of arthritis if consideration be had for the disturbances of the systems which later arise. The point of view which envisages nervous, physical and mental fatigue, faulty body posture, ptosis, and gravitational strain upon organs, anemia, infection, faulty nutrition and faulty alimentation, as significant factors in the full-blown picture, can be made equally appreciative of minor disturbances along the same lines. The success of measures, based on this point of view, in preventing arthritis, and indeed a host of other disorders, is already well established in the opinion of many and indicates that such measures should be exercised more widely than is now the case.

Need to Distinguish between Atrophic and Hypertrophic Arthritis.—In considering a synthesis of therapy in arthritis it is important to distinguish sharply between the two great clinical types which constitute the arthritic syndrome; namely, atrophic and hypertrophic arthritis, diseases of the first and second halves of life respectively. There can be no question of the clinical identity of each of these expressions of the syndrome, but there is by no means so much certitude that either etiologically or pathologically they are wholly and definitely *discrete*.

There is considerable evidence which points to at least some commonalities of origin of the two types of the syndrome, and there is even more evidence which suggests that many of the measures applicable to either type have, indeed, much or equal application to the other type. Much opinion is opposed to the point of view that *infection*, for example, is etiologically significant in hypertrophic arthritis, but no one would deny that, when present, its influence can be important. There is no final evidence that infection may not play a definitely contributory role in true hypertrophic arthritis. We can contrast to this the fact that the supposedly pivotal role of focal infection in atrophic arthritis, hitherto so strongly maintained, has in turn given way to a broader outlook upon the field in which

such infection is only a *contributory* part of the picture. The bases of thought are thus shifting and a tolerant outlook must be maintained.

By the same token, *asthenic build*, *body posture* and *viscer-optosis* are generally regarded as needing consideration and correction in atrophic arthritis, but no one could successfully deny that they may be and frequently are operative in the hypertrophic case, *albeit often hidden* by adiposity and the faulty body habitus of later life.

Treatment of the Two Forms Not Identical.—One could, therefore, direct a series of recommendations which would have, with perhaps varying emphasis, almost equal application to the two great types. In any event, such recommendations, if conservatively framed, could do no harm and at worst would fail to do good. This statement is not meant to be interpreted as implying that treatment of the two great types is identical. This is definitely not the case because, from the outset, great concern must be exercised lest the atrophic case develop fibrotic, cartilaginous, or bony ankylosis, whereas an attitude of almost indifference in this regard can be adopted towards the hypertrophic case. It is also true that the atrophic arthritic presents usually the picture of more acute invalidism. It may be said, parenthetically, that the writer is not among those who believe that the hypertrophic case is necessarily robust. Except in purely traumatic varieties of the disease, the syndrome of hypertrophic arthritis is probably equally systemic in nature.

Bias in Favor of a Given Form of Therapy.—It was stated at the outset that no one feature of therapy could be exhibited with much expectation that the syndrome as a whole could be arrested. The expectation that such a result could be forthcoming has usually arisen from undue enthusiasm. A long perspective in the history of therapy in arthritis reveals that the *great majority* of measures so recommended have been proved in time to be of limited or no value. Because, however, of the apparent benefit which at first often seems to adhere in some of these measures, a strong bias has occasionally arisen for certain given forms of therapy to the exclusion of most others. Indeed, this point of view has not been confined to individuals but has extended even to groups of workers.

For example, the highly significant contributions to arthritis on the part of bacteriologists are everywhere recognized, and yet there have been smaller groups within that field which have regarded the problem of arthritis as a whole from an almost

exclusively *bacteriologic angle*. It was from this premise, in part, that undue emphasis developed upon *vaccines* as the only logical therapeutic corollary to the problem. This somewhat exclusive point of view was more characteristic of what might be called the "morphologic" stage of bacteriology and is waning considerably now that the chemical basis of bacteriology has been widened by the brilliant work of Avery, Goebel, Heidelberger and others.

The point of view which regarded the arthritic as a victim of a "*spray*" of *streptococci*, so to speak, has yielded to that which regards him rather as an individual weakened by systemic imbalance in whom streptococci or other organisms may become influential.

First Step Should Be Attempt to Achieve Equilibrium in Organism as a Whole.—It should follow, therefore, from a dispassionate consideration of the above principles, now widely accepted, that the first step in the care of the arthritic should be an attempt to achieve equilibrium in the organism as a whole. Broken down into its component parts this means achievement of an equilibrium in the chief systems of the body; namely, the *nervous*, *vascular*, *gastro-intestinal*, *locomotor*, and sometimes the *respiratory* systems. The only way in which such a basic approach to therapy of the sick arthritic can be initiated, indeed, is to treat him as other seriously ill individuals are treated, such as the tuberculous, and to *put him to bed*.

Systemic Rest.—It is generally recognized that systemic rest is almost a *sine qua non* in the therapy of the seriously ill arthritic. By preference this means *hospitalization*, and it is important that both the medical profession and society awake as early as possible to the basic significance of this measure. If one were to inquire of dispassionate students that one measure which, in their opinion, could be supposed to have the greatest influence on the syndrome, the verdict would almost certainly be in favor of systemic rest. At one stroke this reaches, to some extent at least, the strain and imbalance of the nervous system, the faulty position and function of ptosed organs, the faulty distribution of blood throughout the body and the improper closure of the finer capillary beds. This last mentioned factor is, indeed, so open to the proper influences that the body heat conserved by the bed covers may alter for the better, almost immediately, the faulty physiology of the lower extremities. In principle, the problem is literally as simple as that in a few selected cases.

The *gastro-intestinal tract* may present anatomic derange-

ment in arthritis, and the redundant and convoluted loops of the large bowel, which sometimes reflect this situation, may experience less tortuosity when the drag of gravity is removed.

The question of *nutrition* is increasingly recognized as having great significance in chronic disease, especially perhaps in arthritis, and this, too, is greatly influenced reciprocally by systemic rest. Not only are all the nutritive requirements then reduced, but betterment is instituted in the way in which the food elements are utilized. Perhaps no field of therapy toward the arthritic has been less appreciated and less developed than that of optimal nutrition. As pointed out in the clinic on Dietetic Considerations, the balance of the various foodstuffs as well as the caloric total may have great significance.

Other Fundamental Types of Therapy.—As the several influences of systemic rest are thus brought to bear, it slowly becomes evident that a step has been taken in rectification of most of the systems of the body and this step should now be followed up with more intensive therapy. Thus the nervous system will benefit by *sedation*, preferably of a gentle nature. The faulty dynamics of the circulation can be greatly influenced by the *application of heat*, not to mention the intelligent use of *physical therapy*. The function of a ptosed stomach showing *hypochlorhydria* can be abetted by the administration of *hydrochloric acid*, and the intestinal tract as a whole may benefit by *lubrication* or administration of a *diet* that is soft but bulky.

No adequate opportunity presents here for fuller development of the general thoughts above expressed. Suffice it to state that there can be no contradiction to the view that any measures of examination or treatment of a vigorous nature will proceed better and have more happy consequences when conducted upon the above premises than they could be expected to have otherwise. By this token, the question of focal infection now comes in for consideration.

Focal Infection.—Focal infection dominated the entire field of the arthritides for twenty years or more, although a very small number of students entertained the view and taught their students that the problem as a whole could not be expected to be solved along these lines alone, in view of the many deviations of physiology to be observed. It is a rather curious commentary upon the present situation that the writer now finds himself in the position of endeavoring, so far as he has influence in the matter, to stem the growth of such an iconoclastic attitude as would sweep away almost all consideration

of the role that focal infection plays in arthritis. The pendulum of medical opinion seems always to be swinging from one extreme to another, and only after years does it come to rest somewhere near a mean point.

It is greatly to be feared that, at the present writing, we are in danger of doing injustice to hosts of arthritics through short-sighted neglect of the limited but definite role of focal infection in this and in other diseases. So significant is this role, always to be understood as having a limited part only, that the mere examination of a subject for focal infection may induce an exacerbation so severe as to reduce the individual to an even lower ebb. This consequence follows even more readily upon attempts at removing focal infection unless they be carried out cautiously and at the right time. It is, therefore, only when a reasonable stage of equilibrium *has been reached* in the seriously ill arthritic that exhaustive procedures for determining focal infection should be entered upon. Any necessary further imbalance of the arthritic organism as a whole will be much less disastrous if, like the aged subject of prostatectomy, an optimal physical equilibrium has been obtained beforehand.

The profession as a whole is yet far from realizing that *infection in the gums* may be and perhaps usually is more influential than is infection in the *apices of the teeth*. The latter can usually be picked up by x-ray examination alone. The former may require the trained inspection of the dentist in addition to adequate x-ray examination. Infection in the *gall-bladder* is usually better detected than it is in the *prostate*, and several prostatic massages may be necessary to determine the presence of infection there.

It is probable that no steps in the direction of controlling or removing focal infection should be carried out in the early stages of therapy except in *mild* instances of the syndrome. Opportunity should be accorded for the establishment of an optimal equilibrium and achievement of at least some of the benefits which this can bring about. There are, of course, instances in which the obvious ravages of focal infection are so marked that no option remains but to proceed at once with whatever measures may be necessary. Such cases are relatively rare. On the other hand, there are many instances in the writer's records in which well-intentioned removal of focal infection at the early stages of therapy of a mild case, then precipitated for the first time a serious and devastating attack of arthritis.

General Sequence of Treatment.—Inasmuch as the present article deals primarily with coordination of treatment and not with the development of any one phase of treatment, it may be well to present here a plan which attempts to outline a general sequence to be followed in average cases. This outline is not to be interpreted rigidly. It may be said, however, that if the necessity should arise of planning on a large scale for a great multitude of severe arthritics, such as might be expected among soldiers if the United States were again to go to war, a rough but useful working plan of initial procedure would be the following:

1. Rest, systemic as well as local.
2. Sedation and/or stimulation.
3. Optimal nutrition in the refined sense earlier discussed.
4. Proper gastro-intestinal function.
5. Examination of the blood and body chemistry.
6. Time for establishment of a general equilibrium.
7. Examination for foci of infection.
8. Medication, such as iron, arsenic, nux, etc.
9. Treatment of foci, conservatively.
10. Use of physical therapy, conservatively—meaning chiefly heat, gentle massage, postural exercise.
11. Orthopedic help.
12. Psychic re-education.
13. Last, if at all, vaccines, gold, etc.

It is not, of course, to be supposed that adherence to this simplified plan would necessarily reach successfully every case of arthritis, but it could confidently be expected that the majority of patients would respond with gratifying results if the details in such a regimen were carried out faithfully. Indeed, during the last war the plan of treatment in 400 cases of arthritis studied intensively by the writer and his associates centered around some features of this regimen and achieved significant consequences. The reader must be cautioned, however, that mere *titular* familiarity with the above headings no more assures the rewards of intelligent therapy than reading a book on golf assures playing a round in par. It should also be observed that in addition to the above *broad* recommendations, certain features of therapy mentioned, such as the *administration of heavy metals, the use of vaccines, etc.*, sometimes require specific and intensive emphasis.

Gold, Vaccines and Drugs.—Thus the exhibition of gold in the arthritic syndrome is now perhaps the most widely practiced of the newer measures of therapy. Like all heavy metals, however, *gold is intoxicating* and may have serious reactions.

The mortality in one of the early series, in which larger doses were given than is now practiced, was as high as 3 per cent, and the Council on Pharmacy and Chemistry of the American Medical Association has refused official sanction of gold salts in either tuberculosis or arthritis. It is therefore obvious that measures carrying any element of danger should come late rather than early in any well-considered scheme of therapy. Not only will the danger of intoxication then be minimized because of a general betterment of the background which the individual presents, but in the majority of instances such measures *may not be required at all*.

This is equally true of *vaccines*, and the considerable obloquy directed toward the use of vaccines might not have developed to the extent that exists had a better therapeutic chronology been exercised in respect to them. Vaccines have a limited though definite place, but the writer has long since arrived at the viewpoint that the spectacle of an arthritic being treated at the outset of therapy by such measures as vaccines and nonspecific protein injections, usually implies ignorance of the field as a whole. There are few cases in which it is sound to require the sick arthritic to develop, at the expense of the organism in general, antibodies whose specificity at best is problematical. The chronic arthritic presents an unusually delicate equilibrium and, if he be subjected to radical steps of any kind early in therapy, not only may the success of that line be jeopardized, but the success of any other may be also and the individual plunged even deeper into the slough of despond.

The use of *drugs* in the arthritic syndrome has constituted one of the most abused phases of therapy. One of the few that have stood the test of time is the group represented by the *salicylates*. These should be used to meet emergencies chiefly, and it is important to realize that in large doses over a long period of time, a psychopathic state may be engendered, much as in addiction to the opiates. *Opiates* should never be given to arthritics. Use of them is nearly always a confession of ignorance and futility. Anodynes shortly cease to be necessary as the arthritic achieves the equilibrium discussed.

One of the first lessons in caring for the arthritic is to learn the importance of helping him to bear the burdens under which he already suffers. This can nearly always be achieved more or less successfully on the basis of the viewpoint entertained above and the conservative sequence of therapeutic steps above outlined.

Reversibility of Arthritis.—The processes of arthritis are, at least in some part, reversible. This is clearly evidenced by the fact that nearly everyone has experienced at one time or another some rheumatic disability in the form of a stiff neck or sore joint which recovers after the use of a little aspirin. That this same process also obtains in principle, even in advanced cases, is not adequately appreciated.

It is nevertheless true that, except for permanent bony changes which are, of course, irremediable, much can be accomplished as a rule, and sometimes apparent marvels may be achieved, through measures which bring about such a restitution of various imbalances, both locally and systemically, as to make *reversibility* possible. Perhaps nowhere else in medicine is better illustration given of the fact that Nature's reparative processes are nearly always available if not negatived by "drugs" and can, usually, be counted upon to function if given an adequate opportunity. It is sometimes necessary to bring before the medical mind again the accepted truth that, at last analysis, *Nature does most of the work* in any case. This is not to be interpreted as a *laissez-faire* policy, because such an attitude almost invariably leads to progressive and downhill crippleddom. When alleged "spontaneous arrest" does take place under such a policy, and this in the opinion of the writer is very rare, there are usually observable in the joints, as a result of chronicity, such gross deformities as to have inspired some one to refer to them, aptly, as "those sterile memorials to a Pyrrhic victory." The time to control the disease is *early*, before such harm is done, and that this is possible in a high percentage of cases has been demonstrated, and is being demonstrated daily, in the Clinic of the writer and his associates.

COMMENT AND SUMMARY

The lesson to be learned by the practitioner who would care efficiently for his arthritics is that the problem must be mastered *in all its details*, that *no single measure* of therapy is to be relied on alone, and that *harmonious coordination* of the agencies available to us is a prime essential if therapeutic discord is not to result.

It is of the highest importance that the laity as well as the profession appreciate the significance of long sustained *hospitalization*; or the equivalent of this, if there is any. Perhaps the greatest difficulty with which the writer has to deal in the therapy of arthritics is their unwillingness to carry on suf-

ficiently long the reparative processes which have become inaugurated. When patients feel better, they think they can do equally well at home. This is rarely true. There must be opportunity for convalescence once started to become "crystallized," so to speak, before a strain is put upon it. The writer frequently illustrates this to his patients by comparing their situation to that of a broken leg; six weeks are required for union and liberties taken with immobility will prevent union. In the case of the arthritic, immobility of physiologic equilibrium must be equally maintained, at all costs. The natural interests centering around the home, children, friends and the telephone may induce such a leak of energy as to undo weeks of physiologic "splinting" of the arthritic as a unit. When the favorable tide is thus interrupted it cannot necessarily be caught again at the flood. All trainers of athletes and horses understand this principle. A man or horse scheduled to race on a certain date cannot break training for ten days and then "carry on" again where he left off. Usually he must go back, perhaps to early training. This is even true of so simple a matter as a course of arsenic which has been interrupted by overdosage or omissions. The "build-up" here involves a definite clinical process which, once interrupted, may never be equally achieved again.

The profession and the laity alike have long recognized that the practice of medicine is partly an art. This must be true by definition, since we can never expect to know all that is included in the field of applied biology; and this, at last analysis, constitutes "medicine." The writer is fully persuaded that if there be such a thing as "the art of medicine" it finds one of its brightest exemplifications in the successful handling of arthritics. Any art which has to deal with psychic as well as with somatic manifestations cannot be learned in a day or practiced by rule of thumb.

The care of arthritics may some day be reduced to a "tour de force," though the varied nature of the problem offers small expectation of this. Until then, the profession and society alike may properly expect that those who care for arthritics should understand the many subtle deviations of physiology which constitute the disease and the measures necessary to bring these deviations into line.



CLINIC OF DR. L. G. ROWNTREE

FROM THE PHILADELPHIA INSTITUTE FOR MEDICAL RESEARCH
IN THE PHILADELPHIA GENERAL HOSPITAL

THE RESULTS OF VARIOUS FORMS OF TREATMENT IN ADDISON'S DISEASE*

TODAY I wish to present a case of Addison's disease of two years' duration and discuss with you the results of various forms of treatment which have been employed. This case is of more than ordinary interest in that the patient has been subjected to many forms of therapy; it is also of interest because of the presence of gynecomastia in addition to the typical manifestations of morbus addisonii.

Early in the course of the disease much difficulty was encountered in establishing the patient on an adequate regimen. In fact, during the first six months it was necessary to hospitalize him on four different occasions. Subsequently, in the last year and a half, he has continued well, and is ambulant, happy and contented though he has not been fully rehabilitated, at least not to the extent I would like to see nor to the degree I have seen repeatedly in cases in which patients are treated with the cortical extract prepared at Princeton by Professor Swingle. However, only once in the last eighteen months has it been necessary for this patient to re-enter the hospital, and then because of a mouth infection incident to the faulty eruption of a wisdom tooth and not for the treatment of Addison's disease *per se*.

It will therefore be interesting and instructive to follow this young man through his various hospital experiences and to see unfold a form of therapy which has brought to him a great measure of relief and a fair degree of rehabilitation.

* This represents part of a clinic given before the Junior and Senior Students at the Jefferson Medical College this spring at the kind invitation of Professor Hobart Reimann.

The author wishes to express his gratitude to the American Philosophical Society for financial support from the Daland Fund.

Case History:

The patient, S. N., a white male twenty-one years of age, was admitted to the Presbyterian Hospital on August 16, 1938, complaining of great weakness, especially in his legs. Neither his family nor his past history revealed anything of significance. His father died three years earlier of pneumonia. His mother is living and well. He seems to have escaped all the diseases of childhood and has undergone no operations of any kind.

The patient is single, and had attended college for two years up to the time of onset of his present trouble. During his last summer vacation he was engaged in field work on a Government project concerned with a survey of the Japanese beetle. He felt well until a few weeks before his first admission to a hospital when he began to notice easy exhaustion and extreme weakness, especially of the lower extremities. This increased to the point where he could no longer work. Then began what might be referred to as his hospital career.

He was admitted first to a hospital in Gettysburg, Pennsylvania, and after two or three days' observation he was dismissed, so far as we know without diagnosis or specific treatment of any kind.

His second admission was on August 16, 1938, to the Presbyterian Hospital, Philadelphia, on the service of Dr. James Talley.* Here were noted his weakness, exhaustion, loss of weight from an original 163 to 130 pounds, nausea, vomiting and marker pigmentation of the skin. Physical examination revealed the unnatural brown color of the skin and the increased pigmentation of the face, arms, and creases of the hands and feet. The genitalia were almost black. There were numerous black freckles and nevi scattered over the skin surface. The gums revealed a bluish-gray pigmentation and a few pigmented areas were found on the inside of the mouth on the buccal mucous membrane. The blood pressure was 84 systolic and 50 diastolic.

The laboratory findings for the most part were negative. The urine showed a trace of albumin and an occasional red blood cell. The erythrocytes numbered 5,500,000. The blood urea nitrogen was 34 mg. per cent, and the blood chlorides 466 mg. per cent. Roentgen studies excluded pulmonary tuberculosis and calcification was lacking in the adrenal areas.

A diagnosis of Addison's disease was made and the patient was placed on eschatin therapy, up to 10 cc. weekly, together

* This patient was subsequently seen in consultation with Dr. Joseph T. Beardwood.

with large amounts of sodium chloride orally as well as intravenously. On August 26, ten days after admission, he was dismissed somewhat improved.

On October 1, 1939, the patient was hospitalized for the third time and was then suffering from a mild crisis and vomiting of two days' duration. The systolic blood pressure was 92. He was given 20 cc. of eschatin, and intravenously 400 cc. of 3 per cent sodium chloride and 200 cc. of 10 per cent glucose solution. He responded promptly; nausea and vomiting ceased and he felt somewhat stronger. Treatment had to be continued, however, and he required as much as 29 cc. of eschatin on one day. Later, other forms of medication were added: vitamins C and B, liver extract and dilute hydrochloric acid. The vitamin C tolerance test was positive, as was also the chloride test for Addison's disease. At the end of October he was discharged, having gained 3 pounds. He was sent home on 3 cc. of eschatin and 15 gm. of salt daily, in addition to cevitic acid, iron, vitamin B, gastrin and belladonna.

In November the patient consulted a local physician who guaranteed to cure him with one injection. Subsequent to its administration the patient gradually fell into a collapse and so was returned to the hospital for further care.

On his fourth admission, on November 18, 1939, the patient was in crisis; he weighed 109 pounds and his systolic blood pressure was 72 mm. of mercury. At this juncture I saw him for the first time; I administered 5 cc. of Swingle's cortical extract and an infusion of 400 cc. of salt solution. Thereafter he was given 3 cc. of this extract daily, which was reduced later to 2 cc., along with sodium salts by mouth and also vitamin C, 25 mg. daily. The patient reacted satisfactorily and underwent a rapid recovery. He was dismissed in good condition on December 11. Subsequently he was given 3 cc. of eschatin daily together with plenty of sodium chloride. On this regimen he has done splendidly. He has regained his strength and his weight has increased to 150 pounds. He has had no further crises and no special difficulty other than a severe infection of the gum associated with the eruption of a wisdom tooth. This necessitated the services of a maxillo-facial surgeon and the patient was hospitalized for one week; the specific treatment was increased temporarily. Otherwise the patient has remained ambulant and has reported to the Philadelphia Institute for Medical Research at intervals of two to three weeks.

After having this bird's-eye view of the whole situation it should prove instructive to go back and consider first the diagnosis and then the various remedies, the amounts used and the results obtained.

DIAGNOSIS OF ADDISON'S DISEASE

Can we be certain that this patient has Addison's disease? Yes! In this respect I feel quite certain. He presents his story, which involves all the *cardinal manifestations* of this disease: progressive asthenia; gastro-intestinal irritability, with anorexia, nausea and vomiting; loss of weight; typical pigmentation of the skin, of the lingual and buccal mucous membrane, together with black freckles scattered over the skin surface; feeble heart action, especially as heard with the stethoscope; and low blood pressure. This combination of symptoms almost clinches the diagnosis, especially if it occurs in a patient who has had tuberculosis, which fortunately is lacking here. Complications, however, often confuse the picture and result in failure to make a correct diagnosis.

Laboratory findings may be of importance in questionable cases: (1) demonstration of melanin in the skin by biopsy; (2) decrease in the sodium content in the blood below 130 milliequivalents; (3) increase in the blood urea, nonprotein nitrates, sulfates and potassium in the blood; (4) decrease in the blood volume and hemoconcentration; (5) decrease in basal metabolism; (6) roentgenologic evidence of calcification in one or both adrenal areas.

Where doubt still exists, resort may be had to: (1) the effects of restricted sodium intake; (2) effects of a high salt diet; (3) the administration of cortical hormone as a therapeutic test.

In arriving at a diagnosis difficulty is often encountered in relation to *pigmentation*. The greatest difficulty is on racial grounds: Ethiopians, Orientals, American Indians, Levantines and Latins normally show pigmentation which, in light-skinned individuals, would be characteristic of Addison's disease. In the Nordic, the pigmentary quartet, dermal, buccal and labial pigmentation with the presence of jet black freckles, is practically pathognomonic.

In *differential* diagnosis, metallic poisoning must be excluded, particularly lead, arsenic and silver. In acanthosis nigricans, the pigmented areas have the appearance and the feel of velvet rather than of satin, as is found in Addison's disease. The discovery of abdominal malignancy is of primary

importance. Hemochromatosis should be recognized through the presence of sugar in the urine and the enlargement of the liver. Pregnancy sometimes offers a diagnostic problem. Scleroderma may offer some difficulty, because it is frequently accompanied by skin pigmentation suggestive of Addison's disease. In all these diseases, *skin biopsy* should prove helpful. Leukoderma may accompany Addison's disease, and its presence does not exclude the existence of the latter. Carotinemia and jaundice can be recognized through the presence of the abnormal pigmentation in the serum. Chloasma, malaria, exophthalmic goiter and vagabond's disease should offer no undue difficulty. Extreme weakness from such other causes as neurasthenia or post-influenzal exhaustion are frequently considered early in the course of the disease.

In this case, however, the evidence appears clear-cut. At present and after the expiration of two years, we can assert with certainty that the patient really has Addison's disease.

TREATMENT

Now let us consider the various forms of therapy that have been employed with this patient.

Eschatin.^{*}—This constitutes the backbone of treatment in this case. It has been utilized throughout the entire time of two years except during crises and for a brief period when other remedies have been employed for one reason or another. Once the period of adjustment was passed, the patient has remained reasonably well on a dosage of 3 cc. daily. However, in the *earlier* days of his illness and in *crises* larger amounts, of from 20 to 29 cc. daily, have been needed. The results, though satisfactory, have not been dramatic and rehabilitation has not been complete. Though ambulant, the patient has not been markedly euphoric or ambitious and has worked but a few days during eighteen months. In his present state I believe that he would be capable of carrying an easy job on a half-time basis.

Sodium Salts.—These have been employed throughout and have been of great value in helping maintain normal health and in reducing the hormonal requirement. The amounts taken have fluctuated between 5 and 15 gm. daily, depending on the patient's clinical condition. In time of crisis, hypertonic salt solution has been employed in large amounts and has proved to be life saving.

^{*} We are indebted to one of my other patients (W. G. McC.) for financial aid and making available constantly, adequate amounts of eschatin for the treatment of S. N.

Combined Eschatin and Salt Therapy.—This has kept the patient in relatively good health, ambulant and free from crises over a period of eighteen months. However, it has not established rehabilitation on as complete a basis as desired.

Vitamin C.—Vitamin C, ascorbic or cevitamic acid, represents the glycuronic acid isolated from the adrenal glands by Szent-Gyorgyi about a decade ago. Through his courtesy we had the opportunity of utilizing this material at that time in the Mayo Clinic. In the opinion of this patient's former attending physician, treatment was more effective when vitamin C was employed. Hence it has been continued throughout two years.

In this connection it might be stated in passing that two years ago we seriously attempted to employ vitamins C and B, and glutathione in the treatment of Addison's disease. While the regimen proved decidedly helpful for some weeks, adrenal insufficiency gradually became more and more marked, necessitating a return to the use of cortical hormone and salt.

Percorten.—Percorten, 5 mg. daily, was substituted for eschatin, 5 cc., on alternate days on November 15, 1939, with results that were not altogether satisfactory. Within two weeks the patient's mother requested that he be returned to the original regimen. While the patient was unquestionably euphoric, his mother stated that he was also restless, irritable, and in her opinion looked sick.

Examination revealed a definite edema of the face and eyelids, and slight edema of the lower extremities. The patient's blood pressure had fallen almost to shock level: 80/60. He had lost his appetite, was dizzy, and in addition he had an urticarial lesion at the point of one injection. Consequently he was returned to eschatin and later refused further trial of percorten.

Percorten is a commercial preparation of desoxycorticosterone acetate which has been heralded by many as the vital hormone of the suprarenal gland. It was isolated from the gland, later synthesized and introduced into treatment by Reichstein. Striking as some of the clinical results have been following its use, it does not represent fully the hormone of the adrenals. Its use in sesame oil in doses of 5 to 20 mg. daily has been attended by some failures, some catastrophes, as well as by many brilliant successes. Although it has been and still is being employed in Addison's disease, either by injection or in some instances implanted as a pellet in the fatty tissues beneath the skin, neither its efficacy nor its safety has been established. Desoxycorticosterone acetate should, therefore,

be considered as being in the stage of clinical investigation. Eventually it may play a large role in the treatment of Addison's disease.

The Cortical Extract of the Suprarenal Gland.—This extract, prepared by and supplied to us for experimental study by Professor Swingle, was used in this case on several occasions. During the patient's third admission, when large amounts of eschatin failed to restore him completely, cortical hormone was employed, at first in doses of 5 cc., later in doses of 3 cc. for ten days, and finally 2 cc. daily, with most gratifying results. Because of lack of supply he was subsequently returned to eschatin treatment in amounts of 5 cc. daily. Cortical hormone was employed satisfactorily again, in the emergency at the time of the mouth infection accompanying the eruption of a wisdom tooth. It was likewise employed for a few days immediately following the trial of Percorten.

This preparation of cortical extract has yielded to date the best clinical results obtained in Addison's disease. It is water soluble, non-irritating locally and non-toxic. With its continuous use and the employment of adequate amounts of salt in six successive unselected cases of Addison's disease, I have seen most remarkable results: the average survival has been seven years and the average duration of treatment five years.

Concentrates of this preparation (triple and quintuple) are now being used in some of our cases, so that injections of small amounts at intervals of two to three days suffice in most cases to keep the patients almost fully rehabilitated and to prevent the development of crises.

A Glycerol Preparation of Cortical Hormone.—This preparation was given by mouth to this patient, 4 cc. four times a day, for a period of two weeks. The preparation was not distasteful and the patient maintained his excellent clinical condition. In fact he claims that he has never felt better than when taking this form of treatment. For obvious reasons, the amounts needed and the excessive cost, the experiment could not be continued for a longer time.

Upjohn's Preparation.—Recently, Upjohn's preparation of cortical extract has been substituted for eschatin in an effort to see whether or not this patient can get along on 1.5 cc. on alternate days of the former instead of 3 cc. of the latter.* Upjohn's preparation is said to represent 50 dog units per cc., and eschatin but 25. To date the patient is satisfied with his

* Under these conditions the clinical improvement was not sustained, the patient returning, on his own initiative, to treatment with eschatin.

progress, though sufficient time has not elapsed to justify a decision as to the relative value of these two products.

Many other drugs have been prescribed for this patient from time to time, especially during crises, but none of them was specific, crucial, or of any true fundamental value. Only adrenal products and sodium salts have really served his needs.

GYNECOMASTIA

The co-existence of gynecomastia in this case is to me of singular interest. As you all know, sex anomalies are commonly encountered in certain tumors of the adrenal cortex: pseudohermaphroditism in congenital lesions, pubertas praecox



Fig. 206a.—Gynecomastia.

in early childhood, and virilism and hirsutism with tumors in the adult. Here, in this patient, we find a well marked gynecomastia which in all probability is the result of a deranged chemistry and a disturbed function of the suprarenal glands. In this connection it is well to realize that in a considerable number of instances Addison's disease has co-existed with clinical manifestations of adrenal tumor. It would appear that tumors of the adrenal, by pressure or by some other process, at times may give rise to adrenal insufficiency, and thus the clinical picture of Addison's disease may accompany the pathognomonic picture of adrenal tumor. In this case the fluctuations in the course of Addison's disease and the administration of all of the various preparations of the adrenal gland have failed to influence the existing gynecomastia.

Now that the chemistry of some of the cortical hormones is known, it is of the greatest significance to learn of their close chemical relationship to the male and female sex hormones. In fact it now appears reasonable to expect that the sex anomalies encountered in tumors of the adrenal gland will find their explanation eventually, in part at least, in the marked chemical similarity of the adrenosterones, androsterones, estrones and progesterones. The bisexual nature of the adrenal anlage constitutes another factor.

SUMMARY AND CONCLUSIONS

In conclusion may we state that this patient has been followed for over two years through various methods of treatment. He has done well and probably will continue to do well so long as an adequate supply of good cortical extract is available. Salt therapy has contributed much to his welfare, particularly since its use has cut down the requirement of cortical hormone.

You will note that the patient still remains moderately pigmented. This will probably continue to be the case, as pigmentation probably represents a disturbance primarily in epinephrine metabolism, the pharmacologic agent secreted by the adrenal medulla. The administration of adrenalin to the point of tolerance, as it was employed in the old Muirhead regime, brought about marked depigmentation. Since pigmentation is of minor importance, it has not seemed wise to subject our patient to this form of therapy.

The modern treatment of Addison's disease is much more effective than measures employed in the past. It brings about not only marked rehabilitation, but it also definitely increases the time of survival. With these modern methods of treating Addison's disease, the life of the patient is relatively comfortable and prolonged, and the work of the doctor concerned is made much easier. There is no doubt but what we are witnessing true progress in the management of Addison's disease.

CLINIC OF DRS. HARRISON F. FLIPPIN AND JOHN S. LOCKWOOD

FROM THE PHILADELPHIA GENERAL HOSPITAL, AND THE
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DEPARTMENT OF SURGICAL RESEARCH, THE SCHOOLS OF
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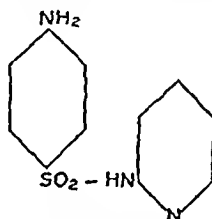
SULFATHIAZOLE AND SULFAPYRIDINE IN THE TREAT- MENT OF PNEUMOCOCCAL PNEUMONIA AND MENINGITIS

THE discovery of the effectiveness of sulfapyridine in pneumococcal infections has reopened the entire field of chemotherapy in pneumonia and in other diseases caused by the pneumococcus. Since its introduction three years ago numerous clinical reports have unquestionably established its therapeutic effectiveness, although it is generally recognized that sulfapyridine is not an ideal drug because of certain toxic reactions associated with its use. Within the past year there has become available a new sulfanilamide derivative, *sulfathiazole*, which is as effective in pneumococcal pneumonia as sulfapyridine, and at the same time less toxic. Our own clinical experience with sulfathiazole, combined with other encouraging reports which have appeared, leads us to believe that it will probably replace sulfapyridine as the principal therapeutic reliance in pneumococcal diseases.

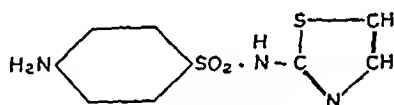
Sulfathiazole.—Sulfathiazole, 2-(p-aminobenzenesulfonamido) thiazole, synthesized by Fosbinder and Walter¹ and Lott and Bergeim,² is the thiazole analogue of sulfapyridine. The term, sulfathiazole, has been adopted as a nonproprietary designation for this drug by the Council on Pharmacy and Chemistry of the American Medical Association.³

Experimental Observations.—Studies *in vitro* by Lawrence⁴ showed that sulfathiazole was superior to sulfapyridine in its bacteriostatic action upon pneumococci of Types I, II and III. The therapeutic effectiveness of this drug against experimental infections in mice has been investigated by

McKee, Rake, Greep and Van Dyke.⁵ If 1 per cent of sulfathiazole or sulfapyridine was incorporated in the diet of mice infected with pneumococci Types I, II, III, V, VI, VII, VIII, XIV and XXVI, the two drugs showed equal protective effects. The report of Van Dyke, Greep, Rake and McKee⁶ showed that sulfathiazole is more rapidly absorbed and excreted by mice, rats and monkeys and undergoes less conjugation in rats and monkeys than sulfapyridine. These workers found that sulfathiazole was no more toxic than sulfapyridine when the drug was administered in therapeutic amounts with the food of mice. Furthermore, sulfapyridine given to rats and monkeys for from fourteen to fifty-seven days was found to be more toxic than sulfathiazole. The principal toxic effect was the occurrence of albuminuria and hematuria in some animals.



Sulfapyridine



Sulfathiazole

Long, Haviland and Edwards,⁷ in studying the acute toxicity of the compounds in mice, found that sulfathiazole has a relatively low degree of toxicity as compared to sulfapyridine.

Clinical Observations.—*Pharmacology.*—Sulfathiazole is absorbed more readily than sulfapyridine from the gastrointestinal tract and is excreted more rapidly in the urine.⁸ Following the intravenous administration of a 5 per cent solution of sulfathiazole sodium, recovery of the drug in urine is practically quantitative. Absorption of sulfathiazole sodium by rectum is slow and only 10 per cent is recovered from the urine within twenty-four hours. Patients receiving sulfathiazole by mouth show appreciably lower concentrations of both free and acetylated drug in the blood than do patients receiving equivalent amounts of sulfapyridine.⁹ Animal

studies suggest that sulfathiazole is not conjugated to the same extent as sulfapyridine. This low conjugation has not been entirely consistent in humans, but in most of the patients the percentage of conjugation has been lower than that observed with sulfapyridine. An important difference between the two drugs is that the concentration of acetylsulfathiazole in blood is closely related to that of free sulfathiazole, whereas no relationship is noted between free and acetylated sulfapyridine. Also, much less sulfathiazole appears in the urine as acetylsulfathiazole than is the case with sulfapyridine.

TREATMENT OF PNEUMOCOCCIC PNEUMONIA

Therapeutic Effectiveness.—In a comparative study of the therapeutic effectiveness of sulfapyridine and sulfathiazole in pneumococcic pneumonia,⁹ it was found that the effects of the two drugs on final mortality were approximately equal. Two hundred adult patients treated with sulfathiazole showed a mortality of 11 per cent, as compared to 15 per cent in a comparable group which received sulfapyridine. Sulfathiazole did not bring about a critical fall in temperature within twenty-four hours as frequently as did sulfapyridine, but the number of drug-induced "crises" within forty-eight hours was similar for the two drugs. Likewise, a return to a normal temperature did not occur as rapidly with sulfathiazole as with sulfapyridine, but the average number of hospital days for the two therapeutic agents was the same, namely 13.4 days. Secondary rises in temperature with sulfathiazole appeared to occur less frequently than with sulfapyridine.

Complications.—The incidence of complications of pneumonia has been definitely reduced with the use of sulfapyridine and, in our experience, comparable results have been obtained with sulfathiazole. *Massive pleural effusions*, necessitating therapeutic aspiration, occurred in 4 per cent of our entire series of pneumonia patients, but only 1 per cent developed *empyema*. The presence of frank pneumococcic empyema demands surgical intervention, as chemotherapy alone is ineffective in the treatment of suppurative lesions. It has appeared that sulfapyridine or sulfathiazole treatment will permit the absorption of serous pleural effusions without aspiration or other interference. Individual patients developed *endocarditis*, *otitis media*, *phlebitis* and *metastatic abscess* as complications in our series of 200 pneumonia cases.

Toxic Reactions.—In general, the toxic effects of sulfathiazole are similar to those caused by sulfapyridine, but occur

less frequently and with less severity. The most frequent toxic reactions from sulfathiazole are *nausea* and *vomiting*. As a rule they appear during the first twenty-four hours of therapy. However, the vomiting associated with sulfathiazole is usually mild and occurs in only 20 per cent of patients, as compared to the more severe and frequent (60 per cent) vomiting which accompanies sulfapyridine therapy. Rarely does the vomiting in sulfathiazole treated patients become so severe as to necessitate stopping the drug. This advantage is of decided importance in the management of patients suffering from pneumonia. When vomiting is persistent it is advisable to replace water and chlorides by intravenous administration of saline solutions, in order to prevent hypochloremia and dehydration.

Toxic effects involving the *urinary tract* have constituted one of the most important complications of therapy with either sulfathiazole or sulfapyridine.⁸ Microscopic *hematuria* occurs in approximately 10 per cent of pneumonia patients receiving either drug. Gross hematuria, which is observed in 1 per cent of sulfapyridine treated cases, has as yet not been encountered by us with sulfathiazole. The associated microscopic hematuria is probably explained in part by the presence of urinary crystals composed of the acetylated fraction of either drug. Unless a considerable number of red blood cells are detected, or evidence of ureteral blockage is apparent, cautious treatment may be continued. Crystals of acetylsulfathiazole were frequently seen in the voided urine and were found at autopsy in the renal pelvises and tubules of one of our patients who died with an endocarditis. *Anuria*, caused by sulfathiazole, has not been encountered by us but we note rather frequently a transient reduction in urinary output during therapy. We feel that the possibility of serious renal damage from sulfathiazole must be borne in mind. If the urinary output tends to decrease markedly the patient should be given additional fluids and, if immediate return of renal function does not occur, the drug should be stopped.

Dermatitis occurs in about 3 per cent of pneumonia patients treated with sulfathiazole. These skin eruptions may be maculopapular, urticarial, or may simulate the clinical appearance of erythema nodosum and be associated with pain and tenderness of the joints. It is usual for fever to occur in conjunction with these drug rashes. *Conjunctivitis*, apparently caused by sulfathiazole therapy, is occasionally seen. The development of dermatitis or conjunctivitis necessitates the withdrawal of the drug.

The diagnosis of *drug fever* in pneumonia patients is a difficult one to make unless a skin rash accompanies the fever. We have encountered what we believe to be drug fever in about 3 per cent of patients. In the absence of other complications associated with pneumonia it is best to discontinue the drug for at least twenty-four hours, as the fever will usually subside within this time if it is due to the medication. *Toxic psychosis* caused by the drugs is also a difficult diagnosis to make. About 4 per cent of our patients developed varying degrees of mental confusion which we attributed to the use of sulfathiazole. Since most of these patients were seriously ill we did not discontinue therapy until the infection was under control.

In the majority of patients the *white blood cell count* tends to drop during the first forty-eight hours of sulfathiazole treatment. White blood counts below 5,000 are observed in about 3 per cent of patients, with the granulocytes falling below 50 per cent in only 0.5 per cent of cases. So far, in our experience, *agranulocytosis* has not been encountered. A progressive *neutropenia* demands daily blood studies and, if the patient's condition warrants, the drug should be withdrawn. So far, this has not been necessary. The *red blood count* and *hemoglobin* likewise fall in a number of cases, but, in view of the fact that pneumonia patients are frequently given extra fluids after admission in order to correct dehydration, it is difficult to evaluate this apparent secondary anemia. If the hemoglobin is below 60 per cent, blood transfusion may be given without stopping chemotherapy. *Acute hemolytic anemia* has not as yet been seen in patients treated with sulfathiazole, but should this complication occur the drug must be stopped and blood transfusion instituted immediately.

Hepatitis, due to sulfathiazole medication, has not yet been observed, although a number of pneumonia patients have clinical or subclinical *jaundice* on admission. The development of toxic hepatitis secondary to sulfonamide therapy demands immediate cessation of drug administration.

A review of these toxic manifestations indicates that the more severe toxic reactions, such as serious renal involvement, blood dyscrasias and dermatitis are infrequent with sulfathiazole therapy. However, the danger of severe toxic reactions increases with the prolonged use of the drug and is greater in patients with chronic organic disease accompanying the acute infectious process. In the treatment of pneumonia we may expect a low incidence of severe toxic effects, as most

patients require no more than 25 to 35 gm. of the drug, extending over a period of approximately five days. However, when using sulfathiazole in diseases requiring treatment over a longer period of time, one may expect a greater incidence of serious toxic reactions.

Contraindications.—In our experience the only possible contraindication to sulfathiazole treatment is a history of a previous *sensitivity to sulfanilamide* and its derivatives as manifested by drug fever, gross hematuria, dermatitis, hemolytic anemia, neutropenia or jaundice. Even in spite of such a known sensitivity, it might be advisable, if the pneumonia is severe, to administer the drug and watch for toxic effects. The presence of jaundice, anemia or leukopenia before treatment is started does not contraindicate drug therapy. We know of no medication which cannot be given to patients receiving sulfathiazole.

Routine Management.—*Dosage.*—As soon as the diagnosis of pneumonia is established and specimens for routine laboratory studies (blood count, urine, sputum and blood culture) are collected, sulfathiazole is given immediately. An initial 3-gm. dose by mouth is repeated in four hours and then followed by 1 gm. every four hours thereafter (unless signs of severe toxicity develop) until the required total dosage has been administered. Treatment on this dose schedule is continued until the temperature remains normal for forty-eight hours and definite clinical improvement is evidenced. In general, the *total dosage* of sulfathiazole is 25 to 35 gm. depending on the day of the disease when treatment is started, the presence or absence of bacteremia, the spread of the infection, and kidney function. It is impossible to make hard and fast rules regarding dosage, as each patient must be handled as an individual case. In certain instances, when a rapid elevation of blood level is desired, a 5 per cent solution of *sulfathiazole sodium* (0.06 gm. per kilogram of body weight) in sterile distilled water, can be given intravenously as a supplement to oral therapy. Where the patient is unable to cooperate to the extent of taking oral medication, it is possible to give the drug through a nasal tube placed in the stomach.

Fluids.—It is important in the management of pneumonia to maintain an adequate fluid balance. At least 3000 cc. of fluids daily should be given, either by mouth or parenterally (a urinary output of 1000 cc. daily is desirable), in order to facilitate the excretion of the acetylated fraction of the drug by the kidneys.

Alkalis.—The administration of alkalis with sulfathiazole is of uncertain value. In some instances it seems to reduce somewhat the associated nausea and vomiting but appears to have little or no effect upon maintaining the solubility of excreted drug by keeping the reaction of the urine near neutral. The routine use of soda bicarbonate or sodium citrate in amounts equal to that of the drug is therefore optional and not imperative.

Serum.—The advisability of administering type-specific serum in addition to sulfathiazole is still a controversial subject.¹⁰ However, we believe that cases in which drug treatment has failed to bring about the expected clinical response within thirty-six to forty-eight hours should be given the benefit of combined therapy. Here again, the physician must treat each patient as an individual, and should give serum earlier when confronted with an overwhelming infection or bacteremia. When administering serum the usual preliminary sensitivity tests, conjunctival and intradermal, are always performed. If these prove negative, after twenty minutes, further intravenous testing with undiluted serum (1 cc.) is carried out. If, after seventy minutes, no untoward reaction has occurred, the patient is given an initial dose of 100,000 units of undiluted type-specific serum intravenously, followed by further injections of serum when necessary.

Sulfathiazole Blood Levels.—It is difficult to say what constitutes an adequate concentration of free sulfathiazole in the blood. In our experience, we have obtained equally good therapeutic results with low as with high levels. It is reasonable to believe that, if a free level of 5 mg. per cent is maintained, one should expect satisfactory results. Levels exceeding this limit have been shown to be associated with a greater frequency of vomiting. Likewise there exists a relationship between high concentration of acetylsulfathiazole and hematuria. Several factors are responsible for individual variation in blood concentrations, such as drug absorption, kidney function, and state of hydration.

Precautions.—When using sulfathiazole one must recognize its toxic possibilities and should follow the patient very closely. Signs of jaundice, drug fever, skin and conjunctival reactions are to be looked for. Repeated blood counts and urine studies for evidence of neutropenia, anemia, hematuria and urobilinuria are important. In certain instances it is helpful to have blood chloride and blood urea nitrogen determinations performed. A fluid intake and output chart should be

kept on each patient. A recurrence or spread of the infection will occur if treatment is discontinued too early. Not infrequently the initial clinical improvement proves to have been deceptive.

TREATMENT OF PNEUMOCOCCIC MENINGITIS

The effective antibacterial action of sulfapyridine has been most convincingly demonstrated through its successful use in pneumococcic meningitis, as prior to the introduction of the sulfonamide compounds this disease was almost 100 per cent fatal. Favorable reports appeared with the use of sulfanilamide, but subsequent experience indicates that sulfapyridine is more effective against this type of infection and is the drug of choice in the treatment of pneumococcic meningitis. However, in view of experimental studies with sulfathiazole and its clinical use in pneumonia, it seems reasonable to assume that this newer compound may prove equally effective in the treatment of this disease. At this time sufficient clinical data are not available to permit an evaluation of sulfathiazole in meningitis. In this paper we wish to discuss certain principles involved in the application of sulfapyridine therapy to pneumococcic meningitis and to emphasize certain practical features in the handling of such cases.

Pharmacology and Action of Sulfapyridine in Pneumococcic Meningitis.—Although in a general way the absorption, distribution and excretion of sulfapyridine is similar to that of sulfanilamide, certain important *differences* exist. Being only one tenth as soluble, sulfapyridine is more slowly, and perhaps less completely, absorbed. The blood concentrations obtained with oral administration of standard dosages of sulfapyridine are extremely variable among individual animals and patients, and the levels are usually considerably lower than those obtained with sulfanilamide. While this has not appeared to constitute an obstacle to the effective use of the drug in pneumonia, it might be of more consequence in meningitis, when high blood and spinal fluid concentrations of the drug are particularly desirable. This apparent limitation may be partially overcome by the intravenous administration of a solution of the sodium salt of sulfapyridine. In this way the blood concentration may be regulated with greater accuracy and sufficiently high blood levels obtained. We do not yet know what constitutes an "adequate" blood level in meningitis, though experimental work would suggest that it is above 8 mg. per cent.

Sulfapyridine passes into the cerebrospinal fluid shortly after appearing in the blood, but the level reached is only 60 to 70 per cent of that in the blood. This is not necessarily of great consequence because it is the existence of antibacterial concentrations of drug in submeningeal tissues, curtailing bacterial invasion, which limits the spread of the process as much as the drug in the spinal fluid itself.¹¹ It is, nevertheless, desirable to have bacteriostatic concentrations of drug in the spinal fluid.

In our experience with the use of chemotherapeutic agents in several different lesions, it has appeared to us that a decisive factor in the action of sulfapyridine is the *chemical state of the tissues and tissue fluid* at the site of infection, with particular respect to the presence or absence of products of tissue proteolysis.¹² In the early diffusely invasive phase of an infection—before the lysis of dead bacteria, tissue cells and leukocytes has proceeded very far—the action of sulfapyridine may assume bactericidal proportions in the body. However, after suppuration develops through localization and tissue breakdown, the action of the drug is far more limited. In the latter conditions surgical drainage or removal of the focus will be an important adjunct to effective therapy. Also, these drugs have only a limited action on bacteria lodged in septic thrombi, and a bacteremia secondary to thrombophlebitis in a large vessel responds far less rapidly to adequate concentrations of drug than one secondary to a diffusely invasive process.¹³

Another consideration in chemotherapeutic action relating to meningitis is the *interference with bacteriostasis* which may occur when bacteria are agglutinated. In unpublished experiments we have found that pneumococci agglutinated by specific serum are not as susceptible to the bacteriostatic action of sulfapyridine in human serum *in vitro* as when agglutinating antibody is excluded. When phagocytes are present this disadvantage may, however, be more than counterbalanced by the capacity of the cells to destroy aggregations of sensitized bacteria.

Routine Management.—Out of the basic considerations just presented we may derive several points which, if consistently recognized in the management of cases of pneumococcal meningitis, will, we believe, contribute to constantly improving results. As soon as the diagnosis of meningitis is established by removal of spinal fluid, sulfapyridine treatment is begun. The routine laboratory tests, including bacteriologic

study of the spinal fluid and blood, should then be carried out. The following plan of therapy is then followed:

1. *Sulfapyridine Dosage*.—Administer an initial dose of 4 gm. and follow with sufficient drug, usually 1 to 2 gm. at four-hour intervals to maintain, if possible, a blood concentration of more than 8 mg. per cent. The drug is given by mouth or through a nasal catheter. If oral dosage is impractical because of vomiting or coma, administer the sodium salt of sulfapyridine in 5 per cent solution intravenously in corresponding amounts at six-hour intervals, until oral administration is possible. In general, treatment is continued on this dose schedule until definite clinical and laboratory cure is established. The drug is then continued in decreasing amounts for at least a week longer, although each case must be handled individually, and no set rules should be laid down.

2. *Type-specific Serum*.—It seems reasonable that measures designed to raise the level of specific antibody against the offending organism will, in all probability, supplement and render more effective the chemotherapeutic effect. As soon as the type is determined, specific antipneumococcus serum is given intravenously. An initial dose of 100,000 units is repeated one or more times depending on the presence of a positive blood culture. There appears to be no indication for serum intrathecally, and, as suggested above, the agglutination of pneumococci in the spinal fluid may interfere with effective drug action.

3. *Lumbar Puncture*.—The ready passage of sulfapyridine into the spinal fluid allows one to avoid frequent lumbar puncture, unless increased pressure symptoms develop, since no intrathecal medication is essential, and the spinal fluid may be assumed to be at least 50 per cent of the blood concentration. Thus it is possible to avoid the potential dangers incident to frequent spinal puncture and excessive withdrawal of spinal fluid. During the first several days of treatment, lumbar puncture may be done daily, but as the cerebrospinal fluid pressure returns to normal and the fluid becomes sterile they are performed less frequently. A satisfactory clinical recovery is usually evidenced by a prompt reduction in the spinal fluid cell count and the appearance of negative cultures. Failure of these two changes to take place within forty-eight to seventy-two hours points rather definitely to the presence of a drug-resistant suppurative distributing focus.

4. *Foci of Infection*.—Since the great majority of cases of pneumococcic meningitis are secondary to infections of

middle ear, mastoid or paranasal sinuses, an intensive search for a possible focus in these areas is imperative. Every patient should be examined by a competent otolaryngologist, and complete x-ray studies of mastoids and paranasal sinuses should be performed with due recognition of the frequency with which the signs of infection in these areas are "masked" by sulfapyridine therapy. The urgency of this step is based on the likelihood that the drug therapy will not influence a primary suppurative focus and that constant refeeding of blood stream and meninges from such a focus will militate strongly against recovery. Marked clinical improvement and sterilization of the spinal fluid and blood stream do not relieve the physician of the necessity for continuation of the search for foci, since the meningitis may become re-established if distributing foci untouched by drug therapy remain.

The slightest evidence of undrained abscesses in mastoids or sinuses demands early *surgical intervention*, even though such findings would not call for surgery in the absence of meningitis. Operative procedures are relatively safe in a patient protected against generalization of infection by sulfapyridine. A failure to recover living organisms on culture of such foci does not mean that inactivated or dormant organisms are not present and that when the drug is discontinued reactivation will not occur with recurrence of meningeal involvement. During the past two years we have treated fourteen cases of pneumococcic meningitis, in five of which recovery has taken place. Looking back on our failures we recognize that several of them were due to delay in instituting surgical drainage of suppurative foci.

5. *Blood Transfusion*.—If the hemoglobin falls below 60 per cent, transfusions of citrated blood are given. The use of repeated small transfusions (200 cc.) may be helpful in the treatment of severe infections such as meningitis.

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UROLOGIC CONDITIONS OF THE FEMALE URETHRA

IN comparison with the complex male urethra, with its numerous extensions and glandular ramifications, the female urethra is simple in construction. Much has been said and written about the former but comparatively little about the latter.

A Symptom Complex Described.—Our attention was first drawn to a symptom complex presented by many of the women appearing for treatment at the Urological Clinic. This symptom complex is one of *frequency or bladder irritation, urgency, nocturia, dribbling and pain referred over the bladder*. It must be remembered that frequency of urination, *per se*, may be the result of some constitutional ailment, such as diabetes or nephritis, and must not be confused with that symptom as arising from pathologic conditions of the urethra and vesical neck. In those instances of constitutional disease with associated frequency of urination, the history of each individual so affected is accompanied by the statement that abnormal quantities of urine are voided at the time of each urination. This is not usually the case where the pathologic change is localized in the urethra or vesical neck. In such instances, small quantities of urine are voided at frequent intervals. Again, in those instances of constitutional disease, urgency, dribbling and referred pain are absent.

In a series of 500 women coming under our observation, it was determined that their conditions fell into the following groups:

1. Urethritis.
2. Cystic or villous formations at the vesical neck.
3. Irregularity of the vesical neck.
4. Stricture of the urethra.
5. Urethral caruncle.
6. Cystocele.
7. Urethral diverticulum.

Many of the women examined had almost complete relief from their symptom complex following observation cystoscopy. This fact led us to attempt a classification of these different conditions as seen locally and to determine their pathologic bases. It is the opinion of the author that a *nonspecific urethritis is responsible for certain definite changes*. As time elapses, this urethritis is followed, after months or even years, by a cystic formation. This cystic change is occasionally followed by a villous formation. The irregularity of the vesical neck may be the result of a sclerosing process following the urethritis. It is not believed that each one of these particular conditions is a clinical entity in itself, but that it is either directly or indirectly the result of urethritis.

The classical *symptoms* of which these patients complain are frequency of urination, with or without burning, urgency, nocturia, referred pain over the bladder, difficulty in starting the urinary stream, incontinence, hematuria and the sensation of incomplete emptying. We believe the suprapubic pain is due to vesical spasm and is a reflex caused by the inflammatory changes involving the vesical neck and also the trigone. The difficulty in starting the urinary stream and incontinence can be attributed to the inability of the vesical sphincter to open or close properly as a result of the sclerotic changes at this location.

In the *examination* of these patients, a bougie à boule and a cysto-urethroscope with water dilatation are routinely employed. The bougie à boule is used for urethral calibration. Its use is quite painless but a local anesthetic is suggested, as cystoscopy always should be done at the time of the examination. The anesthetic of choice is a 1 per cent solution of diothane, although novocaine or cocaine solutions have been used. Authors differ in their beliefs as to the normal calibre of the female urethra. In those individuals who never complain of symptoms referable to the urethra or bladder it has been observed that the average calibre of the adult female urethra is 26 F. We consider a smaller calibre responsible for the symptom complex shown by many women.

CONDITIONS PRESENTING THE SYMPTOM COMPLEX

Urethritis.—The symptom complex portrayed, particularly the frequency, may be so extreme that the individual has a constant desire to void. The frequency may be so acute that only a few drops of urine are passed and this is associated with smarting and burning to a severe degree. In spite of these

irritative symptoms, *cystometry* reveals a normal response or one that tends to hypotonia. In marked bladder infection or cystitis, the cystometric graph is definitely spasmodic and tends to hypertonia.

Few of the women presenting themselves gave a history of a gonorrheal vaginitis. Many of them had a *vaginal discharge*. A culture of this discharge oftentimes revealed the presence of colon bacilli, staphylococci, nonvirulent streptococci and some unidentified diphtheroids. Occasionally, the *Trichomonas vaginalis* was observed. Repeated cultures of *bladder urine* in the cases observed revealed negative results and, for this reason, it is impossible to state the etiologic factor producing such an inflammatory reaction. The persistence of such a condition leads one to suspect the co-existence of a low-grade *chronic infection of the suburethral glands*. The presence of these glands has been demonstrated by such men as Johnson, Sachs, Renner, Folson, Robin and Cadit. It has been conclusively shown and demonstrated that the female urethra contains glands which resemble those of the prostate, but in a less highly developed state. Once these glands become infected the infection of the urethra would persist, due to the contiguity of the structures and the continual escape of infected secretions from these glands.

As observed by the *cysto-urethroscope*, the urethritis occurs as a granular inflammation which may involve the entire urethra, but particularly the posterior portion and the adjacent trigone (Fig. 207). In some instances this granular inflammation surrounds the entire vesical neck; in others, it is localized to the trigone and extends into the urethra. This typical granular appearance has also been seen on the lateral and superior edges of the vesical neck. When the lateral and superior edges are involved, the granular condition is more localized. Multiple localized areas have occasionally been observed, with intervening normal mucosa. These granular inflammatory changes do not show the appearance or the redness that is usually seen in pyogenic inflammatory reactions, but are small, fine, irregularly distributed granular elevations, presenting an appearance not unlike coarse sandpaper. If an attempt is made to look directly down upon these localized areas with the *cysto-urethroscope*, they will not be seen. If the angle of the *cysto-urethroscope* is such that the mucosa is observed at an obtuse angle, however, the elevations will be seen to stand out in relief.

TREATMENT.—The best results in the treatment of urethri-

tis have been obtained by the use of a *bland diet, dilatation of the urethra* and the subsequent *instillation* of one of the albuminates of *silver*. The alkalization of the urine and the oral administration of a urinary sedative such as a mixture of potassium bromide, tincture of hyoscyamus and aqua camphora are routinely employed. Dilatation of the urethra is accomplished by straight sounds, and is done at weekly intervals, increasing the calibre of the sound by one number at each dilatation, over a period of weeks. The urethra in women under fifty can with safety be dilated to 30 or 32 F. However, it should be borne in mind that in women past fifty years of age, dilatation should never be carried to the extreme. In the



Fig. 207.—The cystoscopic appearance of granular urethritis, as observed at the vesical neck.

chronic protracted cases, topical applications of silver nitrate solution have been used successfully as an adjunct following dilatation, the application being made through an open urethroscope, such as was designed by the author a few years ago.

Cystic Formations at the Vesical Neck.—*Polypoid* or *cystic formations* at the vesical neck have been frequently observed (Fig. 208). *Villous formations* at similar locations (Fig. 209), an allied condition, are seen occasionally. The *cystoscopic appearances* are occasionally startling; the picture presented is one of gray, cystic projections. These cysts or polypoid formations are distinct; they may be single but are usually multiple. They are generally seen on the superior or lateral walls of the vesical neck. They do not present an acute

inflammatory appearance at their bases but rise abruptly from a mucosa that is cystoscopically normal in appearance. The



Fig. 208.—Polypoid formations observed at the vesical neck, which is considered a later stage of the granular urethritis.



Fig. 209.—Villous formations observed at the vesical neck, which we consider is the stage following the polypoid formations seen in Fig. 208. Note the marked vascularity of these villous formations.

bases of these cystic formations are broad in comparison to the general contour. They do not appear vascular but as discrete cystic elevations or projections. The *villous* type of forma-

tions present an entirely different appearance. They are considerably longer and are relatively the same size from the base to the tip. They are not discrete but present a shaggy, irregular appearance.

TREATMENT.—The treatment of polypoid or cystic formations is *urethral dilatation*. The age of the patient should always be considered. We feel that it is definitely injurious to overdilate the sphincter of an elderly woman, but in younger women complete relief from symptoms is usually gained by gradual weekly dilatations, ultimately reaching a calibre of 30 or 32 F. After each dilatation, an instillation of mild *silver protein solution* has proved beneficial in the relief of the smarting and burning. The symptoms usually disappear before the maximum calibre is reached, but dilatation in younger women is always carried to 30 or 32 F.

Villous projections should be subjected to *fulguration*. After destruction of these villi by fulguration, dilatation of the urethra is continued to a calibre of 30 or 32 F. Fulguration is definitely a hospital procedure and should never be attempted in routine office practice because of the necessity of an anesthetic and the possibility of a profuse secondary hemorrhage. These villous projections have been removed with the *McCarthy resectoscope*, the instrument employed in trans-urethral prostatic resection in the male, with excellent results. However, one should never cut too deeply through the mucosa. Here again, after removal of the projections, dilatation must be done. It is always well to bear in mind that a urinary sedative, such as a mixture of potassium bromide and hyoscyamus, as well as some of the balsamics, will afford considerable relief to these patients during the course of their treatment. The urine itself should never be allowed to become overly acid, as a concentrated acid urine causes considerable smarting and burning. It is well to keep it more to the neutral or alkaline side and this smarting and burning can be lessened by the use of potassium citrate in one of its many forms.

Irregularity of the Vesical Neck.—Irregularity of the vesical neck has a rather bizarre appearance (Fig. 210). The *cystoscope* reveals the vesical neck to be irregular in outline, instead of the usual smooth contour. This irregularity may be such as to make the vesical orifice present an eccentric contour. The irregularity may be seen at one or more points around the vesical neck but is generally present just lateral to the superior arc. Associated with this irregularity there is a definite narrowing of the vesical neck. This narrowing or contracture

may be extreme, even to a point of producing a sense of resistance as the cystoscope is introduced. As observed, the mucosa is lighter in color than normally seen, presenting a definitely stiffened appearance. This is particularly noted in the area of the irregularity.

We are of the opinion that this contracture and irregularity of the vesical neck is a distinct clinical entity, and do not consider such contracture of the vesical neck to be analogous with, or similar to, stricture of the urethra, as such pathologic change is found *anterior* to the vesical neck. It is in this type of patient that, following cystoscopic examination, complete relief from symptoms is noted almost immediately. Usually in this



Fig. 210.—Marked irregularity of the bladder neck, as observed by the cystoscope. The mucous membrane presents a stiffened appearance, as well as depressions or clefts in the normal contour.

type, the *symptoms* presented are difficulty in starting the urinary stream, pain referred over the bladder area, dribbling of urine, and particularly the loss of a few drops of urine on sneezing or coughing. The age of the women observed with this condition is generally higher than that seen in urethritis or in the cystic types. The *etiological factor* producing such a condition might be a low-grade infection or trauma incident to childbirth, as it has been our experience that, in every instance where this condition was observed, the woman had had one or more children.

TREATMENT.—The treatment of this irregularity of the vesical neck is best accomplished by *dilatation of the urethra*

at weekly intervals, gradually increasing the calibre of the sounds used. Due to the age of the patient and the definite contracture present, it is suggested that the dilatation should not be carried beyond 28 F. This condition, more than any other, always has a tendency to recur, but it has been noted that the time of recurrence after dilatation is always lengthened after each series of treatments.

Stricture of the Urethra.—Stricture of the female urethra has been demonstrated, in many instances, to be the cause of frequency, difficulty of urination and dribbling. The calibre of the normal female urethra has been shown to be 26 F. and the stricture may vary in size from that figure to one of filiform diameter. As in the male, difficulty of urination is proportionate to the diameter of the stricture. The bougie à boule is used routinely in examination of patients, and it is surprising how many women can be classified as having urethral strictures. We do not consider contracture of the vesical neck to be in the same category as urethral strictures but feel that it, in itself, is a clinical entity. Urethral strictures have been demonstrated at many sites along the urethra, from the meatus to the anterior margin of the vesical sphincter. Whether or not stricture is the end result of an infection of the urethra, or the result of trauma, has never been clearly shown.

The *history* of a patient suffering with stricture generally dates back over a period of years. It is always stated that, as time went on, the urinary difficulty became more pronounced, causing considerable straining to start the urinary flow and, once started, there was always difficulty in completely stopping it. The dribbling complained of may occur immediately after the cessation of the urinary act, or it may occur a short time after the individual has assumed an erect position. This dribbling can be explained by the formation of a small dilatation back of the stricture; by siphonic action, the urine will drip involuntarily from the meatus.

The *diagnosis* of urethral stricture is made by the use of a *bougie à boule*. With the characteristic "hang" in stricture the diagnosis is not a difficult one. It has been observed that dilatation was necessary in some instances before the cystoscope could be introduced. In other instances it has been noted that it was impossible to introduce the smallest bougie à boule. Under such conditions a *filiform guide* was introduced. The filiform was threaded, which permitted attachment to a woven urethral bougie or flexible sound. In this manner the urethra

was dilated to such a calibre as to permit the introduction of straight urethral sounds without danger of penetrating the urethral walls.

TREATMENT.—The treatment of urethral stricture is accomplished by gradual *dilatation* with straight urethral sounds at weekly intervals. We consider too rapid dilatation to be injurious. It has been suggested, in those strictures located at the external meatus, that meatotomy be performed, the cut edges being sutured with fine catgut. However, it has been our experience that dilatation will suffice without resorting to operative procedures. Strictures are usually observed in women in middle life, and it is considered unwise to use a greater calibre than 30 F. There is a definite tendency toward contracture of dilated urethral strictures in the male and, for that reason, subsequent dilatation in the female is always considered necessary.

Urethral Caruncle.—Urethral caruncle is a small, florid, moist, vascular tumor occupying the margin of the urethral orifice. The symptomatology is usually one of painful urination and the tumor is very sensitive to the slightest pressure. Occasionally there is bleeding. Urethral caruncle should never be confused with inflammatory or malignant growths at the margin of the urethra.

TREATMENT.—With cocaine as a local anesthetic, the caruncle is grasped by a specially constructed clamp and excised. It may be necessary to put in a suture of fine catgut to control the hemorrhage. Generally, such procedure is not necessary. It has been suggested by various authors that the caruncle be subjected to the *fulgurating current*, under local anesthesia. After any procedure, either excision or fulguration, urethral dilatation should always be done.

Cystocele.—Symptoms of cystocele should never be confused with those of urethral complaints. In a great many instances, women suffering with cystocele will complain of frequency, dribbling and nocturia, but examination will definitely reveal the presence of a sagging or prolapsed anterior vaginal wall. It has been our custom, with all such patients with urinary symptoms, to have the cystocele corrected first and then resort to local treatment of the urethra, if necessary.

Urethral Diverticulum.—Urethral diverticulum in women is a condition that usually follows the trauma of childbirth, particularly a prolonged, difficult delivery (Fig. 211). Patients with urethral diverticula complain of a distinct bulging mass within the vagina, occurring during the time of urination.

They also complain of much smarting and burning. The mass can be made to disappear by pressure in the vagina, which expresses a considerable amount of foul-smelling urine. Coitus is difficult and painful or impossible, due to the location of the tumor at the introitus. On cysto-urethroscopic examination, the opening of the diverticulum may be seen on the floor of the urethra. On examination, the urinary meatus is closed with the examining finger. The patient is asked to void and the bulging mass can be noted to appear within the vagina. A cysto-urethrogram presents a typical appearance.



Fig. 211.—A urethro-cystogram showing the area of the urethral diverticulum.

TREATMENT.—The treatment of urethral diverticulum is accomplished by simple incision of the pouch. This usually results in complete recovery in two to four weeks. Although a number of cures have been reported after conservative treatment such as injection of sclerosing solutions (33 per cent silver nitrate, zinc chloride, etc.), surgery is the method of choice. Careful dissection of the sac and repair of the urethra is not necessary in most cases, as the cicatricial tissue produced has more than sufficient strength to prevent rupture or extravasation.

SUMMARY

1. Nonpurulent urethritis in the female is a definite clinical entity. The symptom complex complained of by women suffering with this condition is a wide and varied one. We believe that urethritis is a sustained infection originating in the sub-urethral glands.

2. Cystic or polypoid formations, as well as villous formations at the vesical neck, are believed to be the end result of a long, protracted, low-grade urethritis.

3. Contracture of the vesical neck and stricture formations in the urethra are two distinct clinical entities, both resulting however from possible trauma and a superimposed, low-grade infection.

4. Urethral diverticulum is occasionally seen. We believe that trauma is a definite etiologic factor in its appearance.

5. The symptom complex of frequency, smarting and burning of urinations, dribbling and referred pain over the bladder complained of by so many women, is a chain of symptoms referred to a definite location. We are of the opinion that all women having these complaints should have a careful and thorough cystoscopic study made of the urethra and vesical neck.

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KETONE ACIDOSIS IN NONDIABETIC ADULTS

According to Peters and Van Slyke,¹ "acidosis may be broadly defined as an abnormal condition caused by the accumulation in the body of an excess of acid or the loss from the body of alkali." Because of the many and complex factors, both physiologic and pathologic, which influence the acid-base balance of the body, a multitude of processes may bring about the state of acidosis as an end result. Such a state exists when either the bicarbonate of the blood falls below, or the hydrogen ion concentration rises above the normal limits.

Conditions Responsible for Acidosis.—Acidosis of the metabolic type, in which "the primary disturbance is in the balance between alkali and acids other than carbonic,"² is encountered in a severe degree in a limited number of pathologic conditions, namely:

1. Severe anoxemia.
2. Severe hemorrhage.
3. Severe exercise.
4. Diarrheal disorders or fistulae of the intestine.
5. Cyclic vomiting of childhood.
6. Toxemias of pregnancy.
7. Administration of acidifying salts.
8. Surgical or traumatic shock.
9. Starvation or carbohydrate deprivation.
10. Renal disease.
11. Diabetes mellitus

When confronted with an acidosis of severe degree, which we may arbitrarily limit to plasma carbon dioxide combining power values less than 30 volumes per cent, it is ordinarily possible to rule out readily all of the above factors except the last three.

Starvation as a Cause.—Whatever the disease producing the acidosis may be, starvation is often present at the same time, and the amount which it contributes to the acidosis must be considered. It is the opinion of Peters and Van Slyke,³ that "the acid retention of starvation never appears to become intense enough to become in itself dangerous; the alkali reserve seldom, if ever, falls as much as 50 per cent below normal." Gamble, Ross and Tisdall⁴ report that in fasted epileptic patients at the height of the ketosis the plasma "bicarbonate is found to be reduced by one third of its usual value." There is listed no case with a plasma carbon dioxide determination below 37 volumes per cent. Lennox,⁵ in a similar study upon twenty-four epileptics and two healthy persons, observed a minimal plasma bicarbonate of 33.2 volumes per cent in one patient, but the average low value for the entire group approximated 45 volumes per cent. From existing reports the conclusion thus appears warranted that starvation of itself will not cause acidosis with a carbon dioxide value as low as 30 volumes per cent.

Diabetic Acidosis with Blood Sugar Normal.—The presence of a marked hyperglycemia, ketosis and low carbon dioxide makes the diagnosis of diabetic acidosis evident. However, the finding of normal blood sugar in an acidotic patient in a single examination at the time of admission to the hospital does not necessarily exclude diabetes. Serious consequences can occur if this is not kept in mind. The most frequent, but not the only, circumstance which accounts for this normal blood sugar is that the patient has already received insulin before entering the hospital. Three cases are summarized below in which patients with clear-cut evidence of diabetes were admitted in acidosis accompanied by normal blood sugar:

Case I.—W. P., male, white, aged seventy-two, was admitted 7/15/31 for standardization. Laboratory findings were: blood sugar, 272; CO₂, 45; blood urea nitrogen, 13. Treatment was standardized at 8-0-0 units of insulin. The patient was readmitted 11/12/31, 10/13/32 and 1/20/33 because of furuncle of the nose, an abscess on the wrist and furuncles of the forehead, and diabetes. His final admission was 10/8/33, at which time the laboratory reported: blood sugar, 96; CO₂, 26; blood urea nitrogen, 20. The patient was comatose, cold and perspiring; respiration was slow and deep, the breath had an acetone odor, the eyeballs were soft, the skin dehydrated, the liver enlarged and nodular, and foul, tarry material passed from the rectum. The patient received 150 gm. of glucose by vein and 95 units of insulin. He died in eight and one-half hours. Postmortem report: primary adenocarcinoma of bile ducts (Type IV) and extreme portal cirrhosis.

Case II.—W. S., male, white, aged twenty-three, was admitted 7/13/32 at 11:00 P. M. Laboratory findings were: blood sugar, 103; CO₂, 30; blood

urea nitrogen, 11. The patient had been experiencing nausea and occasional vomiting for four days. He had been taking insulin, 10-0-10. No insulin or glucose was given during the night following upon hospitalization. Next morning at 7:00 A. M. the findings were: blood sugar, 364; CO_2 , 22 (to resident's discomfort). The patient was discharged taking 49 units daily.

Case III.—S. W., female, colored, aged sixty-two, was admitted to the hospital 10/16/32, with blood sugar 100 and CO_2 , 32. She had experienced abdominal discomfort and occasional vomiting for five days, during which period she had eaten nothing. She was markedly obese. A diagnosis of diabetes was considered, but erroneously was given up because of the blood findings. Glucose and saline were given, but no insulin. On 10/19/32 the patient was transferred to the Metabolic Ward; eighteen hours after last glucose, blood sugar of 30 and CO_2 , 9. She died nine hours after transfer.

Acidosis in Nondiabetic Adults.—While a normal blood sugar may be present under unusual circumstances in a diabetic patient in acidosis, we have also encountered patients in severe acidosis with normal or hypoglycemic blood sugars and normal blood urea nitrogens, who have the clinical picture of diabetic coma, but whose subsequent course proved the acidosis to be due neither to diabetes nor to kidney impairment. A summary of nine of these cases follows:

Case IV.—H. A., female, colored, aged thirty-two.

First admission to Metabolic Division, Philadelphia General Hospital, 12/13/34; discharged 1/5/35.

For two weeks the patient had had a cold and cough. Thirty-six hours prior to admission she began to "hurt all over." For twenty-four hours she had vomited almost continuously. For eighteen hours she had breathed deeply and was hard to arouse.

On entry the patient was semistuporous and restless, with acetone on breath and Kussmaul breathing. Heart, lungs and abdomen were normal. Her temperature was normal and blood pressure was 108/80. Blood findings were: sugar, 127; CO_2 , 19; urea nitrogen, 19; white cells, 19,100. Urine—acetone + + + +, diacetic acid + + + +. After twenty-four hours the blood sugar was 100; CO_2 , 52. Patient had received 208 units of insulin, 400 gm. of glucose, 6400 cc. of normal saline, and 35 gm. of sodium bicarbonate by mouth.

12/27 Glucose tolerance test, giving 1.75 gm. of glucose per kilogram of body weight:

	Blood sugar	Urine sugar
Fasting	50	0
1½ hour	120	0
1 hour	157	0
2 hours	156	0
3 hours	79	0

Fasting blood sugars remained normal on unrestricted house diet and no sugar was present in twenty-four-hour specimens of urine.

Second admission 4/5/35; discharged 4/26/35.

The patient complained of recent difficulty in retaining food. She had vomited and felt weak on several occasions. During ten hours before admis-

sion she had vomited fourteen times. She had pains in her back and abdomen. She was mentally clear. No abnormality was noted except that the liver edge could be palpated 4 fingerbreadths below costal margin.

Blood findings were: sugar, 88; CO₂, 19; urea nitrogen, 13; plasma chloride, 576; white cells, 14,600. Urine—acetone, +++++; diacetic acid, +++++; glucose, 0. After twenty-four hours the blood sugar was at 109; CO₂, 56. The patient had received no insulin; 160 gm. of glucose; 4300 cc. of normal saline; 32 gm. of sodium bicarbonate.

4/12 Bromsulfalein test; 35 per cent retention at thirty minutes.

4/15 Gastric analysis with histamine—no free hydrochloric acid and no total acid above 2 in any specimen.

4/25 Glucose tolerance test (one hour, two dose method):

	Blood sugar	Urine sugar
Fasting	88	0
½ hour	148	
1 hour	156	0.5 gm.

4/8 to 4/18 on a diet of protein, 60; fat, 200; carbohydrate, 50, the urine remained free of ketone bodies and CO₂ did not fall below 54.

4/19 to 4/26 Blood sugar normal and urine free of sugar on unrestricted house diet.

Third admission 5/19/35; discharged 6/13/35.

On 5/18 nausea and lassitude developed, the patient vomited, and became very thirsty; breathing became rapid, deep, and finally stertorous. The patient was drowsy but could be aroused; Kussmaul breathing and acetone on breath were noted; the liver edge could be palpated 4 fingerbreadths below costal margin. Laboratory findings were: blood sugar, 100; CO₂, 13; blood urea nitrogen, 12; white blood cells, 18,800. Urine—acetone, +++++; diacetic acid, +++++; glucose, 0. During the first six hours of treatment the patient received no insulin or glucose; 6500 cc. of normal saline and 25 gm. additional NaCl; 30 gm. of sodium bicarbonate. At six hours the blood sugar reading was 122; CO₂, 13. Between the sixth and thirtieth hour the patient received 340 gm. of glucose; 4300 cc. normal saline; 1500 cc. of Hartmann's solution; 18 gm. of sodium bicarbonate. At thirty hours the blood sugar reading was 216; CO₂, 41. A urine specimen at thirty-two hours contained no acetone bodies. At fifty-eight hours the blood findings were: sugar, 113; CO₂, 63; urea nitrogen, 8.

5/29 Response of blood sugar to adrenalin test: Fasting, 86; 15 minims adrenalin (H); ½ hour, 100; 1 hour, 159; 1½ hours, 163.

Diet 6/3 to 6/6 —protein, 60; fats, 150; carbohydrates, 30.

6/7 to 6/11—protein, 40; fats, 250; carbohydrates, 30,
with small doses of whiskey.

	Blood		Urine	
	Sugar	CO ₂	Acetone	Diacetic
6/8	76	46	0	0
6/9	66	41	+++	0
6/10	76	45	+++	+++
6/11	85	45		

Fourth admission 1/22/36; discharged 2/5/36.

The history and physical findings at this time were almost identical with those of previous admissions. The blood sugar reading was 88; CO₂, 14;

blood urea nitrogen, 13; plasma chloride, 576; white blood cells, 19,500. In eleven hours the patient received no insulin, 1500 cc. normal saline with 30 gm. glucose by clysis and 1400 cc. normal saline with 150 gm. of glucose intravenously; no sodium bicarbonate. At the eleventh hour the blood sugar was at 260; CO_2 , 21. At the thirteenth hour 500 cc. of $\frac{1}{2}$ molar sodium lactate was started intravenously. At the twentieth hour the blood sugar reading was 176; CO_2 , 63.

1/30 Serum cholesterol, 158; ester, 47 per cent.

Fifth admission 9/14/36; discharged 10/9/36.

The patient had not eaten for three days and had suffered from vomiting and diarrhea. She was mentally clear. Laboratory findings were: blood sugar, 75; CO_2 , 13; blood urea nitrogen, 11.

Blood Serum

Total base	128.2 milliequivalents (normal 150-160)
Total anions	
Cl	102.0
HCO_3	5.5
Proteinates	17.8
Inorganic PO_4	1.8
Organic PO_4	1.2
Lactate	2.6
	<hr/> 130.9

After forty hours of treatment the blood sugar reading was 97; CO_2 , 44. Patient received 3500 cc. of normal saline and 325 gm. of glucose, but no insulin, bicarbonate or lactate.

9/22 Takata-Ara—00 +++++.

Comment.—During a period of less than two years this patient was admitted five times in profound ketone acidosis without hyperglycemia or azotemia. The course of events leading up to each admission was very similar. She was a chronic alcoholic and bouts of alcoholism usually if not invariably preceded her admission to the hospital. She would eat but little and about two days before admission progressively more severe vomiting would occur. Finally, there were marked dehydration, Kussmaul breathing, acetone on the breath and more or less severe mental confusion. Clinically the picture was identical with that of diabetic coma.

A review of the treatment shows that the acidosis was controlled as well without insulin as with it, insulin having been used only on the first admission. Glucose, however, was essential. During the third admission there was no rise of carbon dioxide at the end of six hours during which she received large doses of sodium chloride and sodium bicarbonate. During the fourth admission the carbon dioxide rose much more rapidly after sodium lactate was added to the previous

treatment of saline and glucose. During the fifth admission neither lactate nor bicarbonate was used and the carbon dioxide rose relatively slowly. The effect of each of the above therapeutic measures corresponds with our experience with the treatment of acidosis in diabetic patients, except of course the use of insulin was not necessary.

This patient returned to her home in the South and we have not been able to follow her. We have not seen any other patient with repeated bouts of acidosis. However, we have seen a number of patients with single attacks, of which eight summaries follow.

Case V.—D. A., female, colored, aged twenty-six, was a patient in the Metabolic Ward from 9/24/34 to 10/4/34. She was known to be a severe alcoholic. She had vomited for four days, and suffered from paroxysmal upper abdominal pain. There was exquisite tenderness in upper abdomen and marked rigidity. Temperature, 98.6° F.; pulse, 105; respiration, 40. An acetone breath was noticeable. The blood findings were: sugar, 137; CO₂, 22; urea nitrogen, 12; plasma chloride, 510; white cells, 14,300. The first urine was lost in enema; the second showed acetone, +++; diacetic acid, +. After twenty-two hours the blood sugar reading was 162; CO₂, 56. The patient had received 70 units of insulin, 270 gm. of glucose (of which 160 gm. were given intravenously), 4680 cc. of normal saline, and 26 gm. of sodium bicarbonate.

9/25 Cholesterol 168, with ester 55 per cent.

9/27 Icterus index, 50; 10/3, 7. The x-rays show normally functioning gallbladder.

The patient was subsequently observed to have the following blood sugar curves, after the ingestion of 1.75 gm. per kilogram of body weight:

	1/18/35	1/17/36	8/5/36
Fasting	96	102	83
½ hour	122	178	146
1 hour	157	224	180
2 hours	142	163	197
3 hours	120	70	82

She was noted to have an enlarged liver, which increased in size as time went on.

Case VI.—L. C., female, white, aged twenty-seven, was a patient in the hospital four times between 1932 and 1935, each time complaining of nervousness, insomnia, anorexia, palpitation, dizziness and pains in the head. In November, 1935, she was in the Psychopathic Ward with a history of heavy drinking for the previous seven months. Repeated blood sugars were normal and there were no significant physical findings.

The patient was admitted to Metabolic Ward 9/28/36 and remained until 11/26/36. She had eaten little and vomited much in recent months, and for four days before admittance had eaten nothing. She appeared acutely ill and dehydrated, and had cherry-red lips, soft eyeballs, Kussmaul breathing and acetone upon the breath. Blood findings were: sugar, 76; CO₂, 13; urea nitrogen, 18; plasma chloride, 492.

Blood Serum

Total base	119.9 milliequivalents (normal 150-160)
HCO ₃	7.0
Cl	84.0

Urine—acetone, + + + +; diacetic acid, + + + +; glucose, 0.

After fifteen hours the carbon dioxide reading was 56. The patient had received 150 gm. of glucose, 3000 cc. of normal saline and 21 gm. of sodium bicarbonate.

11/4 Serum cholesterol 186, with esters 58 per cent.

On an unrestricted diet nine fasting blood sugars ranged between 81 and 98.

Case VII.—J. B., male, white, aged twenty-nine, was a severe alcoholic who had been in the Psychopathic Ward the previous year for alcoholism. He was admitted to the Metabolic Ward 9/16/36 and remained until 10/1/36. He had been drinking heavily for two to three months. During the previous three days he had eaten only one sandwich and had vomited on several occasions. He complained of weakness and burning epigastric pain.

Kussmaul breathing was present, and acetone on the breath. The blood findings were: sugar, 122; CO₂, 21; urea nitrogen, 28; plasma chloride, 528. Urine—acetone, + + +; diacetic acid, + + + +. After 16½ hours the blood sugar was at 200; CO₂, 44. The patient had received 120 units of insulin, 300 gm. of glucose, 3000 cc. of normal saline, and 10 gm. of sodium bicarbonate.

Blood Sugar Tolerance Test 9/19

Fasting	93	2 hours	124
½ hour	137	3 hours	118
1 hour	124		

Case VIII.—R. R., female, colored, aged fifty-nine. This patient had been in the Nervous Ward the previous year because of an alcoholic debauch, having been admitted unconscious. She was admitted to the Metabolic Ward 5/9/37; discharged 5/13/37. She had been drinking heavily for some days. At entry she was deeply comatose. Respirations were slow and deep. Laboratory findings were: blood sugar, 30; CO₂, 31; blood urea nitrogen, 14; serum aceto-acetic acid, trace; serum beta-hydroxybutyric acid, 94 mg. per cent; cholesterol, 294; ester, 51 per cent.

After receiving 50 cc. of 50 per cent glucose intravenously she immediately became restless and noisy, speaking and shouting unintelligibly. The next morning she was alert and rational.

5/11 Icterus index, 16.

5/11 Bromsulfalein, 60 per cent retention at thirty minutes.

Blood Sugar Tolerance Test 5/12

	Blood	Urine
Fasting	77	0
½ hour	115	—
1 hour	126	0
2 hours	102	—
3 hours	80	0

In addition to the above five cases on the Metabolic Ward, we have been privileged to see four cases occurring in patients

on other wards, in which there was a severe depression of the carbon dioxide, not due to diabetes or nephritis.

Case IX.—J. B., female, colored, aged forty, was admitted to the Nervous Ward 6/22/37 (Service of Dr. Joseph C. Yaskin). She had been drinking heavily for three days and had become unconscious the night before admission. At entry she was in a deep coma.

The blood findings were: sugar, 20; CO₂, 35; urea nitrogen, 13. The urine contained acetone and diacetic acid.

The administration of 75 cc. of 50 per cent glucose intravenously caused her to regain consciousness almost at once. It was noted that the liver edge was palpable half way between the costal margin and the umbilicus.

6/23 Serum cholesterol, 153; ester, 65 per cent.

7/7 Takata-Ara, weakly positive.

7/7 Icterus index, 10.

There was no history of any previous similar attack. The patient made an uneventful recovery.

Case X.—H. H., male, white, aged fifty-four, was admitted to the Medical Ward 5/7/38. He had been drinking freely for several months and had been on a debauch for some days. At entry it was noted that he was very confused but could be aroused, that he was emaciated and markedly dehydrated, and had moderate Kussmaul breathing. Blood findings were: sugar, 42; CO₂, 33; urea nitrogen, 13. The urine contained acetone, ++; diacetic acid, 0.

The patient made an uneventful recovery.

Case XI.—S. M., female, colored, aged thirty-four, was admitted to the Medical Ward 11/9/37 (Service of Dr. Trumen G. Schnabel). She had complained of abdominal pain for three weeks, had been vomiting for six days, and had been profoundly unconscious for twenty-four hours. Blood findings were: sugar, 46; CO₂, 15; urea nitrogen, 13. The urine contained acetone, +; diacetic acid, 0; bile pigment, +. The sclerae were icteric.

The patient died nine hours after entry. At postmortem examination acute yellow atrophy of the liver was found.

Case XII.—E. K., female, white, aged thirty-three, was admitted to the Gynecological Ward 2/18/38 (Service of Dr. Catharine Macfarlane). She had complained of indigestion of variable severity for two months. For twenty-four hours she had had severe abdominal pain and vomiting. At entry she was conscious, in a state of collapse, with belly somewhat rigid. Her menstrual history suggested the diagnosis of ectopic pregnancy, which a laparotomy under local anesthesia failed to reveal. Blood taken after glucose had been started intravenously, but before the laparotomy, contained sugar, 166; CO₂, 21; urea nitrogen, 9. The patient died twenty-seven hours after admission. Postmortem examination showed portal cirrhosis with extreme fatty infiltration.

Comment.—Cases IV, V, VI and VII were all sent from the Receiving Ward to the Metabolic Ward with the provisional diagnosis of diabetic coma. Their clinical appearance simulated exactly that of diabetic coma, and the severe acidosis accounted for their symptoms and physical conditions. In

Cases VIII, IX and X, however, the acidosis was less pronounced, but hypoglycemia was present severe enough to produce profound unconsciousness in Cases VIII and IX and mental confusion in Case X.

In view of the fact that in each case, except the last two, acidosis occurred in a patient *addicted to alcohol*, and frequently if not invariably after a debauch, the question arises as to whether alcohol of itself can cause a profound ketone acidosis. Himwich and his associates⁶ reported that in both dogs and human subjects there is a metabolic acidosis due to accumulation of lactic acid, but the tables presented reveal that the carbon dioxide capacity never dropped below 40 volumes per cent, even for prolonged debauches in which the blood lactic acid attained 40 mg. per cent. In no experiment did they find evidence of ketosis.

Our chief purpose in reporting the above cases is to point out that a very severe ketone acidosis can occur in adult patients *who are not diabetic*. Concerning the *mechanism* of the production of the acidosis we can only speculate. The first two patients had enlarged livers, presumably due to fatty infiltration, most of the patients in laboratory tests gave evidence of impaired liver function, and the last two patients were found to have severe liver damage at necropsy. We assume that the liver had a diminished ability to store glycogen and to convert noncarbohydrate substances into glucose. With starvation of several days' duration, the damaged liver could not produce sufficient glucose from noncarbohydrate sources to meet the metabolic requirements. Under such conditions, as Mirsky⁷ has pointed out, *fat metabolism* becomes excessive and ketosis results. This viewpoint is supported, also, by the fact that in Cases VIII, IX, X and XI the patients were definitely hypoglycemic.

Collip⁸ and his co-workers and others^{9, 10} have reported the isolation of an anterior pituitary ketogenic or *fat metabolism hormone* which effected an increased blood level of ketones and urinary output of ketones, but we are not aware of any evidence of pituitary dysfunction in the cases under consideration.

If the combination of liver damage and food deprivation, occurring most frequently in association with acute alcoholism, can cause such a severe ketone acidosis as we have described, the question naturally arises as to why this state is not more frequently observed. To this we have no answer, except that we have diagnosed such cases more frequently since being aware of their existence.

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HYPERTENSION

My object is not to discuss all the phases of this subject, but rather to illustrate, by means of cases, the diagnoses and treatment of the three most common conditions in which hypertension is a prominent manifestation.

Pathogenesis.—The rapid accumulation of new facts pertaining to the pathogenesis of hypertension has thrown a great deal of light on this old and perplexing problem. Much of our knowledge of the subject may be attributed directly or indirectly to the work of Goldblatt. His observations have resulted in a mass of additional experimentation and results which confirm the role of *renal ischemia* in the production of a *pressor substance* which appears to be the direct cause of hypertension. Page has demonstrated the presence of an additional factor which appears to activate the pressor substance. He further finds evidence of an *inhibitor substance* which appears to counteract the pressor substance. This latter substance is supposed to be elaborated by normal kidney tissue. Thus as the supply of pressor substance increases due to ischemia, resulting from advancing kidney disease, the supply of inhibitor substance decreases, due to the loss of normal kidney tissue. This work is largely experimental and is not necessarily the final solution to the problem. The clinical importance of renal ischemia as an etiologic factor is further emphasized by the report of Blackman, who found definite narrowing of the renal arteries, at or near their origin from the aorta, in 85 per cent of 50 cases of essential hypertension. This was in striking contrast to the 50 control cases, in which only slight narrowing was observed in 10 per cent. A number of single case reports have appeared in which hypertension was relieved by removal of tumors or other masses which caused constriction of a renal artery. Likewise, the removal of a single diseased kidney because of pyelonephritis, tumor or infarct has resulted in the rapid return of the blood pressure to normal.

The importance of *urinary infections and obstructions*, as the cause of pyelonephritis and the associated hypertension, has been emphasized by Weiss and Parker. The frequent association of this condition with the toxemia of pregnancy is illustrated in their cases. They stress the extreme variability in the clinical course of pyelonephritis which makes it extremely difficult to recognize in many instances. Furthermore, the infection may remain inactive for many years after the acute stage and its presence may be recognized or suspected only during acute exacerbations. They estimate that 15 to 20 per cent of all cases of malignant hypertension are due to pyelonephritis.

It is obvious that hypertension in the great majority of instances is secondary to an underlying primary condition and is not a separate disease entity. At one time the term "essential" or "idiopathic" was applied to from 80 to 90 per cent of all cases of hypertension. Owing to the recognition that the majority of cases are either neurogenic, endocrine, cardiovascular or renal in origin, the diagnosis of essential hypertension is made less frequently and there is no doubt that it may be replaced entirely. However, for the time being, we are still forced to use it in many instances.

ESSENTIAL HYPERTENSION

The following case is an example of hypertension in which we are unable to find evidence of any underlying primary disease; hence it is designated as essential hypertension:

Case I.—H. M., a forty-eight-year-old married woman, first came to the clinic in 1935, complaining of headache, dizziness and insomnia. Her mother died of apoplexy at the age of fifty-two years. Her father died suddenly of heart disease at fifty-eight years. One sister had "high blood pressure." Another sister had "kidney trouble."

The patient's health had been unusually good, except for measles and mumps during childhood. She had three normal pregnancies and labors. She places the onset of her present illness at the beginning of her menopause in 1934. This was accompanied by marked nervous disturbances and the blood pressure estimation was reported as "high" at that time. Our records show that at the time of her first visit to the clinic in 1935, her blood pressure was 190 systolic, 108 diastolic. The urine was free of albumin; specific gravity 1.028. It contained an occasional leukocyte, but no casts or red blood cells. Her heart was normal in size and there were no cardiac murmurs. Since then she has been a regular visitor to the clinic, and our examinations indicate that her condition has become progressively worse, until it became necessary to refer her to the ward for complete physical rest.

On admission to the hospital, the patient complained of shortness of breath on exertion, dizziness, impairment of vision, nocturia two or three times, and weakness of the left arm.

The physical examination revealed a well nourished white woman lying flat in bed. The skin and mucus membranes were normal in color. There was slight weakness of the muscles of the right side of the face, and weakness of the left arm. There was prominent pulsation of the vessels of the neck. The thyroid gland was not enlarged. The lungs were normal. The area of cardiac dullness was increased to 13 cm. to the left of the midsternal line at the fifth interspace. There were no cardiac murmurs. The rhythm was normal. The second aortic sound was greatly accentuated. The liver edge was felt 2 inches below the right costal margin. The spleen was not enlarged. There was slight pretibial and ankle edema. The peripheral arteries were moderately thickened and tortuous. The blood pressure on the day of admission to the hospital was 230 systolic and 128 diastolic. Since then it has fallen slightly and maintains an average level of approximately 205 systolic and 115 diastolic. The spinal fluid pressure was 310 mm. of water. This was reduced to 250 after the removal of a specimen for examination.

The urine was clear with a specific gravity of 1.010. It contained a slight trace of albumin, an occasional white blood cell, but no red cells or casts. The two-hour specific gravity test showed a fixed low specific gravity with a maximum concentration of 1.015, and a great increase in the volume of the night specimen over the day specimen. The phenolsulfonphthalein excretion amounted to 55 per cent in two hours. The result of the urea clearance test was 65 per cent of the average normal. The blood urea level was 16 mg. per cent. The blood Wassermann and Kahn reactions were negative. The basal metabolic rate was normal.

A roentgenogram of the chest revealed enlargement of the cardiac shadow, which chiefly involved the left ventricle. x-Ray examination of the skull revealed nothing abnormal. The blood count was essentially normal: 4,300,000 red cells, 7,200 white cells, and a normal differential smear. The electrocardiogram indicated left ventricular preponderance, but otherwise was normal. Ophthalmologic examination revealed blurring of both disk margins, arterio-venous compression and narrowing of the arterioles. A retrograde pyelogram produced no evidence of urinary obstruction or disease of the ureter or pelvis of either kidney. Separate specimens of urine obtained by ureteral catheterization were entirely normal and contained only 2 to 4 white cells per low power field. A sugar tolerance test gave normal results.

Predisposing Factors.—The importance of the *hereditary factor* in essential hypertension has long been recognized. In this instance, a sister was known to have hypertension, and it is probable that the father who died of heart disease had hypertension. A second sister had "kidney disease." Certainly most of the members of the family exhibit a tendency to cardiovascular disease.

The patient had been in an excellent state of health until the onset of the *menopause* which began five years ago. The associated vasomotor and nervous manifestations were unusually severe. It is not uncommon to find slight to very high blood pressure which has its onset with the menopause. Frequently, this condition is temporary and promptly subsides after the menopausal symptoms disappear. Occasionally, as

in this case, it persists for years. The prognosis of hypertension coincident with the menopause is usually good.

Diagnosis.—*Hyperthyroidism* can be definitely eliminated as a possible cause of hypertension in this case, by the normal basal metabolic rate and the absence of the other commonly associated symptoms. *Basophilic adenoma of the pituitary* can be eliminated by the negative x-ray of the skull, the normal sugar tolerance curve, and other evidences of the syndrome.

Because of the rapid progress in her illness, we made a special search for evidence of *pyelonephritis*. Repeated urine examinations did not reveal more than a normal number of leukocytes and other formed sediment. Urine cultures were sterile. There is no history of urinary tract disease, such as cystitis, pyelitis or acute nephritis. There has never been any tenderness in the region of the kidneys, and the normal pyelogram excludes disease of the ureters and pelves of the kidneys. The right kidney's lower pole is palpable, but not tender. It is possible, as in the cases reported by Weiss and Parker, that pyelonephritis is present and in a quiescent stage with complete absence of signs and symptoms, and at autopsy the pathologic changes of the chronic stage of the disease may be found. However, in the absence of more positive clinical evidence, we must class it as essential hypertension.

We may assume that the hypertension in this case is due to *primary vascular disease*. Possibly there is sclerosis and narrowing of one or both renal arteries, producing partial renal ischemia, as mentioned above. Unfortunately, it cannot be proved except by surgical exploration; the patient's physical condition and the improbability of finding a unilateral renal sclerosis does not justify such a procedure.

This patient's disease is well advanced, as indicated by the symptoms of *early myocardial failure*, and evidence of an impending intracranial accident. The renal function is maintained by the excretion of an increased volume of low specific gravity urine. Withdrawal of spinal fluid reduced the high intracranial pressure and relieved the associated symptoms, such as edema of the optic disk and muscular weakness of the face and left arm. Generally her condition has improved, and the blood pressure level is lower. However, I expect a rather prompt return of the pressure and symptoms when she resumes her duties.

Prognosis.—The outcome of this case is very uncertain and indefinite. It is probable that it will be terminated by

sudden or gradual myocardial failure or cerebral apoplexy. Renal failure rarely occurs except when it is secondary to cardiac decompensation. The prognosis in essential hypertension is variable. Some of these patients go on for ten or twenty years or longer, with few, if any, symptoms; in others, the progress is rapid and fatal in a few years.

Treatment.—The treatment of essential hypertension in the majority of cases is unsatisfactory. Complete recovery is extremely uncommon. However, by the careful use of the available methods and drugs, much can be done to maintain the majority of these patients in comparative comfort and useful life for many years.

MENTAL HYGIENE.—It is of prime importance that the patient should not regard hypertension as a death warrant and live in mortal fear of apoplexy, heart failure or other terminal events. One should not be too pessimistic in regard to treatment; much can be done to relieve and prevent the various manifestations of the disease. It is important to assure the patient that high blood pressure is compatible with long life. Advise him to divert his attention from his blood pressure and to avoid discussion of the subject with his friends. Worry and anxiety over business or social affairs should be eliminated as much as possible.

REST.—Regular hours of rest and diversion should be encouraged. *Vacations* should be arranged so that the maximum amount of physical and mental rest will be obtained. Winter vacations in the warmer climates will reduce the incidence of upper respiratory infections. *Exercise* should be reduced to walking or playing a few holes of golf. The amount of exercise should be carefully determined for each individual case, depending chiefly on the functional capacity of the circulatory system.

DIET.—Various forms of diet for the relief of hypertension have been suggested and tried. In general, the diet should be arranged with the objects of *reducing weight*, when it is excessive, and of providing adequate amounts of the essential foods—proteins, carbohydrates, fats and vitamins. The harmful effects of obesity in the hypertensive patient is recognized by most clinicians. Not infrequently a reduction in weight is followed by a sharp drop of the blood pressure. This is especially important to the patient with signs of myocardial weakness. Whether the patient loses weight or not, he frequently obtains relief from certain annoying symptoms, notably gaseous distention of the stomach and dyspnea. Suffi-

cient exercise to produce any effect on the weight would result in an enormous increase in the work of the heart and vessels. Such a strain, whether it is sudden or gradual, could readily result in myocardial failure or apoplexy. The only practical and harmless method of weight reduction is the proper regulation of food ingested.

Meat-free diet in treatment of hypertension is no longer considered of value. In fact, the rigid restriction of protein is definitely contraindicated. This is especially true if there is loss of large amounts of protein in the urine. In such instances, protein restriction may result in the production of edema. In the average patient with hypertension, the protein in the diet should be sufficient to supply the normal requirements of the body: approximately 1 gm. of protein per kilogram of body weight. Indeed, there is no scientific confirmation that even excessive amounts of protein are injurious to the hypertensive patient with normal kidney function.

The benefits obtained by rigid salt restriction have not been sufficient to warrant its continued use. Furthermore, such a procedure is an added hardship to the patient, because a salt-poor diet is definitely not palatable. In the absence of edema, the avoidance of excessive salt ingestion is sufficient. This may be accomplished by avoiding salty foods and not adding salt to the food after it is prepared in the kitchen.

BEVERAGES.—There appears to be no harm to the hypertensive patient from an occasional drink of an alcoholic beverage, or from moderate amounts of tea or coffee.

DRUGS.—Drugs, in the treatment of essential hypertension, find their greatest value in the relief of symptoms. The drugs which act by relaxing the vascular system have a transient and uncertain effect. Hypertension alone is not an indication for such medication. Many patients are entirely free of symptoms, and there is no benefit to be obtained by overzealous attempts to reduce the pressure. The reduction of pressure often results in disagreeable symptoms, especially in those cases of long duration, with advanced vascular damage.

Nitrites.—The nitrites depend on their vasodilating effect to reduce an elevated blood pressure. Their duration of action is brief and, in most instances, there is nothing to be gained by their use. They may be used to advantage in the periods when hypertension is highest. They frequently afford relief for certain headaches and for the pain of angina pectoris.

Potassium Sulfocyanate.—Recently excellent results have been reported from the use of potassium sulfocyanate to lower

and steady the level of blood pressure. The use of this drug is not without danger. The toxic symptoms usually observed are nausea, vomiting, and cerebral manifestations such as hallucinations of hearing and sight. The drug should not be administered unless the concentration of blood cyanate is determined at frequent intervals. The best results have been obtained with blood cyanate level between 6 and 10 mg. per 100 cc. Toxic symptoms have been known to occur when the blood level exceeds 12 mg. per 100 cc. of blood. There is no doubt that the administration of this drug results in a lowering of the blood pressure, but the actual benefit to the patient is not sufficient to warrant its use, in view of the possible toxic effects.

Nervous Sedatives.—The nervous sedatives are the most valuable drugs in treatment of hypertension. They are especially useful in those cases in which the patient is nervous, hypersensitive and troubled by insomnia. Frequently, their administration is followed by a moderate reduction of the elevated pressure. Even when there is no change in the blood pressure level, the patient experiences considerable symptomatic improvement. *Phenobarbital* is one of the most useful sedatives. It is most effective when administered in $\frac{1}{2}$ -grain doses, three to four times daily. The frequency and size of the dose of phenobarbital, as with all sedatives, must be regulated for each individual case, so as to abolish nervousness and irritability without causing drowsiness. Combinations of the bromides and barbitals often give the desired effect when either one fails. The effect of phenobarbital may be lost after prolonged administration, necessitating a change to another barbituric acid derivative. Combinations of chloral and bromides may be helpful when other sedatives fail.

Iodides.—I have not seen any beneficial effect obtained by the prolonged administration of potassium or sodium iodide in essential hypertension. It is difficult to determine the value of drugs in the treatment of this condition because of the wide fluctuations in blood pressure which occur without treatment. Likewise, the enthusiasm of the patient about any change in treatment frequently results in temporary improvement.

SURGERY.—Operative procedures, such as renal denervation and adrenalectomy, have not resulted in the desired benefits. Bilateral splanchnic denervation seems to offer better results but, as with any of these operations, a great deal of care must be exercised in selecting suitable cases. This diffi-

cult procedure requires two operations, which are usually conducted two to four weeks apart. Only the early cases without marked vascular damage can be offered a fair chance of improvement.

CHRONIC GLOMERULONEPHRITIS

The following case is illustrative of the onset and course of chronic glomerulonephritis:

Case II.—N. I., a twenty-five-year-old white man, was admitted to the hospital on May 20, 1940, complaining of headache, impairment of vision, and nocturia once or twice. His family history is irrelevant. He had had several attacks of tonsillitis; and at the age of nineteen had a severe attack of scarlet fever which was followed by chronic otitis media. Immediately following this illness, he developed acute glomerulonephritis with edema of the face, and oliguria. The records from the Municipal Hospital show that the urine was highly concentrated, contained a heavy cloud of albumin, many granular casts, and red blood cells. After a long convalescence the edema gradually disappeared, the output of urine increased, and the red cells disappeared from the urine. His blood pressure at that time was 155 systolic, 105 diastolic. Since then, on the several occasions that his urine has been examined, it contained a cloud of albumin. However, he stated that he had been quite well and free of symptoms, except for nocturia, until two weeks ago when he developed a severe infection of the upper part of the respiratory tract which confined him to bed for ten days. This was followed by a persistent headache, puffiness of the eyelids, and a feeling of general malaise.

The physical examination revealed a well developed young man. There was puffiness of the eyelids and the face. There was marked pallor of the skin and mucous membranes. The blood pressure was 210 systolic and 130 diastolic. The area of heart dullness extended 14 cm. to the left of the mid-sternal line. A systolic murmur was present at the apex. The second aortic sound was greatly accentuated. The rhythm was normal. Crepitant rales were heard at the bases of both lungs. The edge of the liver was felt 2 inches below the costal margin. The spleen and kidneys were not palpable. There was slight edema of both lower extremities.

The urine was cloudy and amber colored. The specific gravity was 1.015. It was acid in reaction and contained a heavy cloud of albumin, 5 to 10 white cells and 10 to 20 red cells per low power field. The result of the urea concentration test was 15 per cent of the average normal. Examination of the blood revealed 1,600,000 red cells, 11,000 white cells and 38 per cent hemoglobin. The differential smear was normal. The nonprotein nitrogen was 140 mg. per cent. The blood Wassermann and Kahn reactions were negative. The total proteins of the blood serum was 4.8 per cent. The maximum concentration of the urine was 1.014. Ophthalmoscopic examination revealed several "cotton-wool" areas in both retinas and several small, recent hemorrhagic areas in the right retina. The electrocardiogram indicated left ventricular hypertrophy and some interference with ventricular conduction as indicated by slurring and notching of the QRS complexes in all leads.

Pathogenesis.—The onset of this man's illness with scarlet fever, followed by an attack of acute nephritis at the age of nineteen, leaves little doubt as to the cause of his present

illness. It is justifiable to assume that he has had a *latent type* of chronic nephritis since the acute illness. During this period he has been comparatively free of symptoms, except for nocturia.

His present condition is due to an acute exacerbation caused by an *acute infection* of the upper part of the respiratory tract. This is confirmed by the return of *subcutaneous edema* and *oliguria*. The hypertension first appeared shortly after the acute attack and has become progressively worse during the past eight years. There are also signs of early myocardial failure, pulmonary edema, congestion of the liver, and electrocardiographic findings suggestive of rather advanced myocardial damage. Severe *secondary anemia* is also a part of acute and chronic glomerulonephritis. It is not uncommon for the severity of the anemia to parallel the impairment of renal function. The cause of the anemia is not only due to the persistent loss of blood in the urine, but is probably influenced by depression of the erythropoietic function, and by deficient diet and impairment of gastro-intestinal digestion and absorption.

Diagnosis.—The outstanding differences between this condition, chronic glomerulonephritis, and the former, essential hypertension, may be summed up as follows: urinary findings—albumin, casts and red blood cells. In the former, the urine is clear, little or no albumin, no casts and low concentration. Nitrogen retention is uncommon in essential hypertension, unless myocardial failure is present; in nephritis, its level is almost parallel with the degree of renal damage. Secondary anemia is a prominent factor in glomerulonephritis; rarely present in essential hypertension. The onset of glomerulonephritis frequently follows an acute infection and usually occurs in childhood. The onset of essential hypertension is insidious and is rare before adolescence.

Treatment.—**DIET AND HYGIENE.**—The treatment has consisted largely of dietary and hygienic measures. *Rest in bed* is essential, preferably between blankets to prevent chilling of the skin. The intake of *fluids* should not exceed the total daily output of urine while edema is present. The *diet* should be regulated to compensate for loss of protein in the urine and to maintain nitrogen equilibrium, the minimum requirement of protein being about 1 gm. per kilogram of estimated normal body weight. Much of this protein may be supplied in the form of egg albumin. It is absolutely injurious to eliminate meat and other protein from the diet.

With the great loss of proteins in the urine, the serum proteins must be replaced or low values will contribute to the edema. *Salt* should be restricted as long as there is edema. Even after complete disappearance of edema, salty foods and the addition of salt to the ordinary cooking is contraindicated.

DRUGS.—Drugs in chronic or acute nephritis have very little value. The *xanthine* diuretics rarely increase the volume of urine. The *mercurial* diuretics are definitely harmful. *Digitalis* should be used in the routine manner, if there is evidence of myocardial failure. *Iron* may be helpful if the anemia is severe, as it is in this case. The *nitrites* may be temporarily beneficial for the relief of the hypertension.

CHRONIC PYELONEPHRITIS WITH HYPERTENSION

Pathogenesis.—The frequent association of hypertension with genito-urinary tract obstruction and infection has been recognized for many years. This combination was often observed with prostatic obstruction and cystitis. Following prostatectomy and proper drainage of the infected bladder, it was not uncommon for the blood pressure to return to its normal level. Now it is recognized that such infections often extend to the pelves of the kidney, and pyelitis is invariably associated with pyelonephritis. Such a sequence of events may follow any bladder infection. In the majority of such cases, the patient appears to make a complete recovery; others have an abnormal number of pus cells in the urine for many years and no symptoms until late in life, when they may develop hypertension, which on ordinary inspection appears to be essential hypertension.

This condition has been found to be especially common with *pregnancy*, due either to a previous infection or to an acute infection induced by pressure on the ureters. It is entirely probable that this is one of the causes of the kidney lesion and hypertension in certain toxemias of pregnancy. It does emphasize the necessity for a careful investigation of the urinary tract before and during pregnancy. A preexisting infection of the pelves is almost invariably made worse by pressure from the pregnant uterus on the ureters.

The following case illustrates the sequence of events following an ordinary attack of cystitis which apparently extended to the pelves of the kidneys and resulted in chronic pyelonephritis:

Case III.—R. M., a twenty-seven-year-old colored woman, was first observed in the Outpatient Department in June, 1934. At that time she com-

plained of frequent painful urination, vaginal discharge and backache. The urine contained many white blood cells, an occasional red cell and a trace of albumin. The blood pressure was 125 systolic and 90 diastolic.

In November, 1938, the patient returned to the hospital complaining of headache, insomnia and attacks of dizziness. She gave a history of a miscarriage in March, 1938. She stated that she became very ill during the seventh month of pregnancy, while on a visit to the South, and that she was confined to bed for three weeks before the spontaneous delivery of the dead fetus. Examination revealed moderate increase in the width of the cardiac dulness. A catheterized specimen of urine contained 20 to 30 white cells per low power field and no red cells or casts, and had a specific gravity of 1.015. The blood pressure was 195 systolic and 115 diastolic. After this visit the patient failed to return to the clinic and was not observed again until the present admission to the hospital (February, 1940). On this occasion she complained of blurring of vision, dizziness and headache.

Physical examination revealed a poorly nourished colored female. The area of cardiac dulness extended 11 cm. to the left of the midsternal line. There was a systolic murmur at the apex, and the second aortic sound was greatly accentuated. During the ten days in the hospital, her blood pressure varied from 230 to 190 systolic and 125 to 105 diastolic. The edge of the liver was palpable and moderately tender on pressure. There was slight tenderness in the region of the left kidney. The spleen was not enlarged. There was no obvious change in the peripheral arteries. Examination of the fundi revealed moderate sclerosis of the retinal arteries, with several small "cotton-wool" exudate areas. Edema of both optic disks was present, with an elevation of 1 diopter.

There were traces of albumin in the urine. The number of white blood cells in the urine varied from 20 to 80 per low-power field. No specimens were seen without an abnormal number of white cells. Red cells were absent. An occasional hyaline and granular cast was found on two examinations. The maximum concentration of the urine was 1.012, and there was a marked increase of the night volume over the day volume. The blood count showed a moderate secondary anemia: hemoglobin 72 per cent; erythrocytes 4,100,000 and leukocytes 9,800 per cubic millimeter. The blood nonprotein nitrogen was 78 mg. per 100 cc. The blood Wassermann and Kahn reactions were negative. The urea clearance was 28 per cent of the average normal.

The electrocardiogram showed inversion of the T waves in Leads II and III, with moderate left axis deviation. Cystoscopic examination revealed edema and inflammation of the trigone. A specimen of urine from the right ureter contained 20 to 30 white blood cells per low power field. Urine from the left ureter contained 2 to 5 white cells per low power field. The pyelogram revealed filling defects in the pelvis and calyces and dilatation of the right ureter. The changes in the left kidney were present, but less evident. *Bacillus coli* was cultured from the urine of each kidney.

Diagnosis.—The history of this case leaves no doubt that the patient's illness began six years ago with what appeared to be an attack of acute cystitis. The association of backache with acute cystitis should have suggested pyelonephritis at that time. Like many clinic patients, she failed to return and was not seen again until November, 1938. Then she gave a history of an illness which confined her to bed for several

weeks. The details of this episode are unobtainable because she was not treated in a hospital. However, from her description of the symptoms, it is entirely probable that it was due to pyelonephritis.

On each successive visit to the clinic, we found a higher blood pressure. On every occasion abnormal numbers and clumps of white cells were found in the urine. At present there is definite evidence of chronic pyelitis and disease of the ureters indicated by the roentgenogram. *Bacillus coli* has been cultured from the urine which was obtained by ureteral catheterization. The physical changes are not unlike those usually associated with advanced cardiovascular-renal disease due to other causes, but the pyuria, bacilluria and history of acute attacks of cystitis and pyelitis confirm the diagnosis of pyelonephritis.

Prognosis.—The prognosis in this case may be estimated from the extent of the renal damage and the tendency of the disease to progress. Renal function tests such as the urea clearance, the ability of the kidneys to concentrate urine beyond 1.014, and the high degree of nitrogen retention, indicate extensive renal damage. Retinal hemorrhages and evidence of severe myocardial damage are evidence of the widespread myocardial and vascular degeneration.

Treatment.—The treatment of chronic pyelonephritis with hypertension is *symptomatic* in character. Thus, it is not unlike that usually followed in chronic glomerulonephritis. Every effort should be made to reduce the work of the kidneys to a minimum, and to encourage the remaining functioning glomeruli to carry on the work. Attempts to eliminate the residual infection usually result in additional damage.

It is especially important to recognize signs of urinary tract infection *in their early stages*. Dysuria, frequency and pain or tenderness in the costovertebral angles should suggest the possible presence of pyelitis. The diagnosis can be confirmed by finding pus cells and culturing bacteria from a catheterized specimen of urine. Frequently all symptoms are absent and the condition is only recognized by repeated cultures of the urine.

SULFANILAMIDE.—Sulfanilamide is particularly valuable in the treatment of pyelitis and pyelonephritis in their early stages. Sulfanilamide is administered in 7½-grain (0.5 gm.) tablets, four times daily, preferably after meals. The fluid intake should be reduced to 1200 to 1500 cc. daily. Bicarbonate of soda in 30-grain (2.0 gm.) doses should be given with

the sulfanilamide. At the same time all precautions should be taken to prevent the untoward effects of the drug.

If this treatment proves to be ineffective, as evidenced by the continued presence of pus and bacteria in the urine, the patient should have complete *bed rest*; search should be made for *urinary tract obstruction* which might interfere with proper drainage from one or both kidneys. *Nephrectomy* should be considered when the infection is confined to one kidney. Excellent results, with prompt return of the blood pressure to normal, have followed such a procedure.

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NONRENAL (EXTRARENAL) AZOTEMIA

To the clinical mind, azotemia connotes a pathologic state manifested by certain symptoms; among these an abnormally high level of urea nitrogen in the blood is a predominating feature.

Azotemia is generally thought of in connection with uremia due to structural changes in the glomeruli and secondarily in the tubules of the kidneys. A top normal of blood urea nitrogen of 16 to 18 mg. may rise to from 100 to 500 mg. per cent or even higher. Similar findings may obtain in congenital cystic kidneys, in mechanical obstruction to the flow of urine due to an enlarged prostate, or to tumor or stricture of the lower genito-urinary tract. Doubtless, in these conditions, the azotemia may be explained on the basis of *renal damage*. On the other hand, there have been a number of patients observed in whom the striking laboratory finding has been a high concentration of urea nitrogen in the blood *in the presence of normal kidneys*, both from a physiologic and anatomic point of view. This form of nitrogen retention, the so-called *nonrenal azotemia*, centers around a variety of pathologic states which are integrated with a severe and reversible change in the salt and water metabolism of the body. It is this type of "uremia" that we shall discuss this morning.

The importance of recognizing these states lies in the fact that many of them may be mistaken for a serious renal condition, especially since traces of albumin, casts, and red blood cells are quite often found in the urine. Furthermore, prompt and appropriate treatment of nonrenal uremia may prove life-saving.

ILLUSTRATIVE CASES

Case I.—Urea Nitrogen Retention Due to Dietetic Restriction of Sodium Chloride and Fluids, and Epileptic Convulsions.—Miss L. R., aged twenty-three years. Complaint: convulsive seizures.

This patient suffered her first attack of epilepsy at the age of sixteen, apparently associated with the menstrual cycle, and these attacks occurred thereafter at intervals of two to four weeks. Essential epilepsy was diagnosed and a two-year regimen of fluid limitation and salt restriction had been followed. The evening before admission, she was in a state of "status epilepticus," remaining semistuporous for four days.

Physical Examination: Heart action was decreased and no murmurs were heard. The lungs were clear and abdomen scaphoid in shape and hyperesthetic throughout. All reflexes were depressed. Blood pressure 95/55.

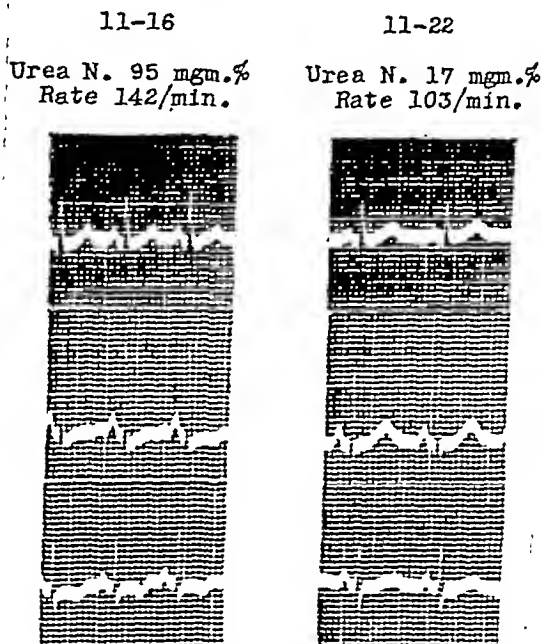


Fig. 212.—Tachycardia and myocardial dysfunction: S-T segment is lowered and T is flat in Lead 2. In Lead 3, S-T segment is arched and T is negative. Six days after illness, electrocardiogram is normal.

Course: The chemical analysis of the blood on the sixth day after admission was rather striking, the blood urea being 95 mg., the nonprotein nitrogen 180 mg., creatinine 7.3 mg., and the blood sugar 135 mg. Three thousand cc. of normal saline were given intravenously, and she reacted well, being able to answer questions intelligently. A day later, she again lapsed into a stupor and 500 cc. of 10 per cent glucose in saline were given intravenously, as well as 1000 cc. of saline by hypodermoclysis. This was repeated again the next day. She showed progressive improvement. The blood urea nitrogen had fallen to 17 mg. per cent, and nineteen days from the date of admission, she

was free from symptoms. Epileptic seizures were again suffered on the 4th, 10th and 15th of December and the patient was discharged on the 19th of December, 1933.

That the chemical findings in the blood were not the result of an acute renal uremia is apparent from the fact that the blood pressure was low, the urine had a high specific gravity, and there were no uremic retinal changes. Furthermore, the administration of fluids and salts decreased the non-protein nitrogen and cleared the patient's mentality. A point of considerable interest was a depression in the S-T segment and diphasic T deflection in the electrocardiogram (Fig. 212). The changes in the S-T segment in the electrocardiogram in this case assume significance in the light of Himwich's experiments on anhydremia with hyperpyrexia in dogs. The tracings, he found, were not unlike those observed in this patient. McCulloch made similar observations in children.

The changes are probably due to partial anoxemia of the heart muscle due to insufficient filling of the coronary vessels, caused by a decreased blood volume and drop in blood pressure. It seems likely that the patient's stupor and the high blood urea resulted from the dehydration due to dietetic restriction of fluids and salts for a considerable length of time.

Case II.—Suppression of Urine and Rising Concentration of Urea in the Blood Due to Adrenal Insufficiency May Mimic an Acute Urologic Catastrophe.—M. K., aged sixty-two years. Complaint: bleeding from the penis and bouts of chills. Four hours prior to admission he had diarrhea and polyuria with blood-stained urine. The day prior to this he had exposed himself to the sun on the beach for about eight hours continuously and soon after developed chills and noted the blood drainage from the meatus.

Examination revealed that the patient was very thin and dehydrated; the tongue was dry and coated, the eyes were sunken, breathing was rapid and shallow, the pulse 120, respirations 30, and the temperature 103° F. Examination of the lungs showed diminished breath sounds throughout and decreased resonance in both upper lobes. The heart was of normal size, the sounds were distant and of poor muscle tone. Blood pressure 70/52. The abdomen was distended; no tenderness, no rigidity, no masses were palpable. A urologic examination by Dr. C. H. Shivers showed a slight increase in size of the prostate; there was no acute involvement of the seminal vesicles; the base of the bladder was normal with no evidence of distention. The kidneys were not felt.

Laboratory Findings: Blood urea nitrogen, 46.6 mg. per cent; blood sugar, 120 mg. Blood count: hemoglobin, 10 gm. or 64.9 per cent. Red blood cells, 3,290,000. White blood cells, 16,250. Polymorphonuclears, 92.5 per cent, nuclear or Schilling index = 1.8, a marked shift to the left (200 cells counted). Small lymphocytes 3.5 per cent, monocytes 2 per cent. Urine was not obtained for analysis.

Course.—It was the clinical impression that the patient was suffering from a surgical kidney. He was too ill to have any further studies made; he was

therefore given prontosin, grains 5, with grains 5 of sodium bicarbonate for four doses. One thousand cc. of normal saline solution was given by hypodermoclysis and 20 cc. of 50 per cent glucose intravenously. Within twenty-four hours the temperature declined to 98° F., the pulse to 80, and respirations to 20.

An examination by Dr. Shivers at that time was reported: "Patient complains of no discomfort today. A distended bladder cannot be palpated. Tympanitic note directly above symphysis. Unable to palpate either kidney; no tenderness bimanually. Tenderness at costovertebral angle on left side. Slight bloody drainage from the meatus. Rectal examination shows no evidence of bladder distention. This man has not voided, according to his statement, since 9 p.m. last evening. No edema of his extremities. Comment:

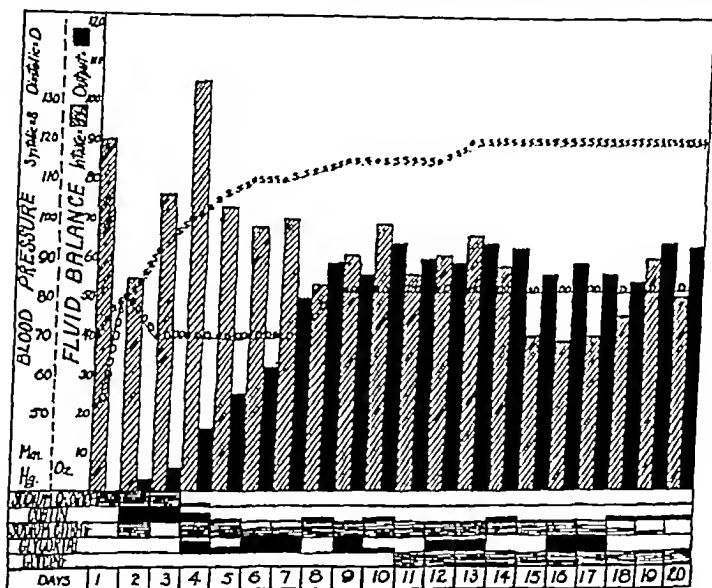


Fig. 213.—Blood pressure and water balance during course of illness. Note the anuria prior to administration of adrenal cortex hormone, and reestablishment of kidney function upon administration of desoxycorticosterone.

renal damage is responsible for our present findings. I would suggest continuing hypodermoclysis, giving 1000 cc. of normal saline today."

Prontosin was discontinued and 1000 cc. of saline was given by hypodermoclysis. The patient complained of weakness and drowsiness. No urine was obtained by catheter. An additional liter of Fischer's solution was given intravenously, with no improvement. He continued to manifest extreme weakness; he had anuria; the blood pressure declined to 60 mm. systolic; the blood urea nitrogen had risen to 75 mg. per cent, and the blood chlorides were 500 mg.

Because of extreme weakness and low blood pressure, one of us (MGW) suggested the possibility of adrenal insufficiency. This impression was strengthened by the finding of a slate-colored area on the inner side of the left cheek

and lower lip. Consequently, the patient was given 10 cc. of adrenal cortical extract (Wilson Laboratories) intramuscularly and was placed on 15 gm. of sodium chloride and 5 gm. of sodium citrate daily. Not being able to procure additional cortical extract for intramuscular use, the glycerin extract of adrenal cortex (glycortal pills) was administered orally, five pills daily. In addition, adrenalin, 0.5 cc. of 1:100, was given at frequent intervals (Muirhead treatment). The clinical improvement was immediate and striking; the blood pressure had risen to 90 systolic and 60 diastolic, and he voided 5 ounces of urine after three days of complete suppression. His blood urea nitrogen, however, had risen to

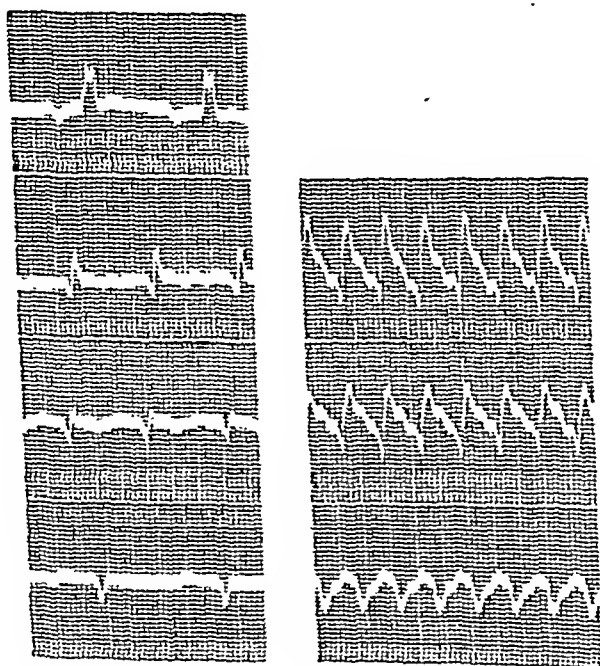


Fig. 214.—Electrocardiogram of M. K., showing ventricular tachycardia, with rate of 196, and coronary thrombosis.

96 mg. per cent. Synthetic adrenocortical hormone (desoxycorticosterone acetate) was obtained, and 5 mg. was given intramuscularly. Twenty-four hours later, patient voided 15 ounces of urine; he felt considerably stronger and, in addition to liquids, he was able to take semisolid food. The following day he received another dose of 5 mg. of synthetic adrenocortical hormone; his blood pressure had risen to 110 systolic and 70 diastolic; he voided 25 ounces of urine, and he felt quite comfortable. He continued to improve on 10 mg. of desoxycorticosterone weekly and a high salt and low potassium diet.

Three weeks later he left the hospital in good condition. The blood urea nitrogen had declined to 18 mg. per cent and the twenty-four-hour urine out-

put was 65 ounces against a fluid intake of 60 ounces. He returned to his place of business and attended to his usual duties for a period of two and a half months. On October 24, 1939, he developed coronary thrombosis with a ventricular tachycardia (rate 196) and he died six days later.

It is to be regretted that no postmortem examination was possible in the case; however, we learned recently that, in 1933, this patient had a train of symptoms (weakness, loss of weight, anorexia, vomiting, low blood pressure, etc.) which responded favorably to the administration of adrenal cortex.

This patient was considered to be suffering from an acute urologic catastrophe because of the anuria, elevated temperature, and rising concentration of urea in the blood. The renal function was restored by the use of cortin and sodium chloride. The anuria was doubtless due to the drop in the blood pressure. According to the studies of Lassen and Husfeldt, urine volumes vary with the fall in the blood pressure. As a result of these studies, the authors feel that the systolic blood pressure of the peripheral circulation need fall but little below 70 mm. before the production of urine would cease entirely.

The fever in our patient might be explained on the basis of dehydration. The blood from the meatus is difficult to account for. There was no evidence of renal tuberculosis and repeated examination of the urine for tubercle bacilli was negative. That hemorrhage from the rectum, vagina, nose and conjunctivae may occur during an acute episode of adrenal insufficiency has been commented upon in the literature. To our knowledge, this is the first time that hemorrhage from the genito-urinary tract occurred in connection with adrenal insufficiency.

TYPES OF NONRENAL AZOTEMIA

Adrenal insufficiency may serve as a prototype for other states of nonrenal azotemia. In all of them the clinical syndrome is not unlike that observed in an acute adrenal insufficiency. The common denominator in all these conditions is the *excessive loss of electrolytes and water*. This fundamental biochemical shift is the background of the subjective and objective symptoms. It may be well to divide these states into two groups.

Group I. Loss of Electrolytes and Water through Apparent Channels.—1. *Loss of gastro-intestinal secretions.*—This may result from severe protracted vomiting in pyloric and duodenal obstruction, hyperemesis gravidarum, gastric tetany, acute and chronic intestinal obstruction, severe diarrhea, and intestinal fistula.

2. *Loss of extracellular fluid and sodium chloride from excessive perspiration.*—This may occur in miners, stokers, and workers in the tropics, in whom heat cramps may result. In some cases extremely high temperatures may develop.

3. *Diabetic coma.*—In acidosis and coma of diabetes mellitus, the polyuria, glycosuria, and vomiting may cause loss of fluids and large amounts of sodium chloride. The azotemia may be thus erroneously attributed to kidney failure.

4. *Restriction of fluids.*—The not uncommon clinical circumstances wherein limitation of fluid and restriction of salts are employed therapeutically are obesity, hypertension, skin and bone tuberculosis.

5. *Postoperative azotemia.*—An increase in blood urea nitrogen is not an uncommon finding postoperatively. On the continent, it has received considerable attention by French investigators. In this country, Derow, and Coller and Mad-dock, have dealt with this subject extensively. The azotemia is usually associated with a hypochloremia. Following an operation, the patient may present a marked hypochloremia and azotemia and yet seem to be making an uneventful recovery. On the other hand, the patient may present grave symptoms, with only a slight hypochloremia and moderate azotemia. The replacement of chlorides has been most gratifying, especially following abdominal operation and prostatectomy. Most of the reported cases in the literature belong to one of these groups. They have been designated by the French as "*Azotémie par manque de sel.*"

Group II. Loss of Fluids and Electrolytes That Is Not so Apparent.—There are other states with nonrenal azotemia in which loss of water and electrolytes through known channels, such as skin, stomach, etc., is not so obvious. They are *burns*, *histamine shock*, and *other shocklike conditions*. In these sodium chloride is immobilized at the site of injury rather than lost. In Addison's disease, there is excretion of sodium chloride even when chloride concentration in the serum is abnormally low. In all states of advanced dehydration there are essential signs of shock; they reflect failure of the body to maintain the blood circulation and blood pressure due to dysfunction of the capillaries resulting in the loss of plasma protein and in a decrease in the volume of the circulating fluids.

There is another group of patients who develop after surgery on the biliary tract a clinical syndrome resembling that under discussion and which is accompanied by a high blood

urea nitrogen level. This is the so-called *hepatorenal syndrome* of Heyd. The causative mechanism of this syndrome is doubtless similar to that of other states of nonrenal azotemia.

SYMPTOMS

Clinically, patients with nonrenal azotemia have in common the following characteristic symptoms: *fatigue, loss of weight, asthenia, decline in blood pressure, dry and slaty-gray colored skin, shallow respirations, disorientation, somnolence* and, perhaps, *coma* in the extreme stage. Another distressing symptom is *abdominal pain*; this is often bilateral and is associated with epigastric tenderness. *Fever*, unexplained on the basis of infection, is a frequent manifestation.

In addition to this clinical pattern, other symptoms will depend largely on the many varied diseases inducing the loss of electrolytes and fluids from the body. These diseases are usually acute and fulminating; the superadded symptoms of the nonrenal azotemia are, therefore, of *short duration*, in contradistinction to the chronicity of uremic symptoms that result from renal failure.

Laboratory Findings.—The outstanding laboratory findings are a *decreased excretion* of urine, which is of *high specific gravity, moderate albuminuria*, with hyaline and occasional granular casts, and a few *red blood cells*. The *chlorides* in the urine are diminished or absent.

The chemical pattern of the blood will depend upon the underlying disease conditioning the loss of fluids and electrolytes. Where there has been simple deprivation of fluid or loss through evaporation, the blood is concentrated with respect to the red blood cells, hemoglobin and serum proteins, and is of high specific gravity. The nonprotein nitrogen, including blood urea nitrogen and, at times, uric acid and creatinine, are elevated, although no significant demonstrable alteration in the kidneys may be observed.

With loss of gastric juice from pyloric or duodenal obstruction, or duodenal fistula, *dehydration* and a state of *alkalosis* result. This is due to the fact that these secretions contain a relative excess of chlorine ion (as HCl) over sodium ion. With loss of gastric juice, there is therefore more than a normal amount of sodium available to form bicarbonate; hence, the carbon dioxide combining power of the plasma is increased.

It is important to bear in mind that the *reaction of the urine* may be strongly *acid*, due to the fact that the alkali is retained and not excreted. Since the concentration of bicar-

bonate is high, and that of chloride is low in the intestinal and pancreatic fluids, it is apparent that, with loss of intestinal fluid (severe diarrhea or fistula), or loss of pancreatic juice through a fistula, a state of dehydration and acidosis will result. The symptoms, as described above, are similar to those associated with adrenal insufficiency and, biochemically, there is a decrease in the CO_2 combining power of the blood with a normal or increased concentration of chlorides in the plasma. When both vomiting and diarrhea occur, the predominating state is more likely to be that of acidosis. In the remaining states of nonrenal azotemia there results some degree of acidosis.

FACTORS OF IMPORTANCE IN THE DEVELOPMENT OF AZOTEMIA

The exact mechanism by which azotemia develops is exceedingly complex; it has been experimentally investigated by many workers, but it still awaits final elucidation.

That, at necropsy, patients with nonrenal azotemia may show very little structural changes to account for the elevated blood urea is well known. Likewise, kidney function studies fail to give convincing evidence of depressed renal function to explain the azotemia. It is partly because of these facts that some European investigators were inclined to attribute the concentration of urea to an attempt on the part of the body to compensate for the low osmotic pressure caused by loss of electrolytes. This explanation would seem to be untenable, since the cells of the body are readily permeable to urea, in contrast to their virtual impermeability to the sodium ion. The rise in urea in the circulation and body fluids, therefore, could not maintain the osmotic pressure compensatory to loss of sodium chloride.

The prevalent thought at present is that the loss of sodium ion is of greater significance in the pathogenesis of azotemia than is the loss of chloride. With loss of sodium from the body there is loss of extracellular fluids and generalized signs of dehydration manifest themselves. With dehydration, there may be excessive breaking down of body protein, a fall in blood pressure, increase in viscosity of the blood and subsequent decreased circulation rate through the kidneys; there is also a rise in plasma proteins due to fall in plasma volume. All these factors may lead to the reduction of kidney efficiency with the resultant urea nitrogen retention.

The possibility of disturbed adrenal physiology playing a rôle in nonrenal azotemia should be borne in mind. In recent

experimental work, Wohl, Burns and Clark found that in hypochloremia and azotemia of high intestinal obstruction, the cortex of the adrenal glands of dogs showed morphologic changes in the zona fasciculata and glomerulosa. Administration of cortin and salt solution, or large doses of salt alone, prevented the structural changes in the adrenals, and the blood urea nitrogen remained normal. It would appear that the altered adrenal gland in hypochloremia, at least of high intestinal obstruction, bears a relationship to the depressed renal function. Loeb, Atchley and Stahl made the pertinent observation that the adrenal cortical substance acts on the kidney to control the excretion, not only of sodium, but also of urea.

TREATMENT

In treating patients with nonrenal azotemia, it is necessary to *replace sodium chloride and water, to adjust the acid-base equilibrium if acidosis or alkalosis is associated, and to treat shock*. Additional measures directed to combat the underlying disease must perforce be carried out, *e. g.*, local therapy to burned areas, etc., and removal of the cause of a pyloric or intestinal obstruction.

Replacement of Sodium Chloride and Water.—*Physiologic salt solution*, containing approximately 0.85 per cent of salt, is the most widely used intravenous solution for replacement of sodium chloride and water. Theoretically, the amount of fluid to be given daily should be equivalent to volume for volume of secretions lost, in addition to about 1500 cc. required for normal kidney function, and 1500 cc. to replace water evaporated from the skin and exhaled through the lungs. It is frequently impossible to know what volume of secretions has been lost, since the patient may not have been under medical observation in the early stages of the disease. In such instances, the estimation of *plasma chloride* values may furnish a guide to the depletion of sodium chloride. Various formulas have been suggested for calculating the total amount of chlorides to be restored to the body. For practical purposes Collier suggested giving 0.5 gm. of sodium chloride per kg. of body weight for every 100 mg. of sodium chloride below the normal plasma chloride level (570 mg. per 100 cc.).

Actually the *best clinical guide* is to give sufficient saline until signs of dehydration have disappeared and excretion of urine containing chloride has been reestablished.

If *continuous venoclysis* is employed, one may give to adults from 2 to 3 liters in twenty-four hours, though 5 liters have

been given with good results. When the loss of salt is greater than is contained in the intravenous saline, *hypodermoclysis* can be used to supplement the venoclysis. If the patient is dehydrated without the loss of salt, *water by mouth* may restore the normal water balance. If water cannot be given by mouth, intravenous administration of 5 per cent dextrose may be successfully used. Not infrequently the first administration of fluids consists of equal parts of physiologic salt solution and 5 per cent dextrose (2.5 per cent dextrose and 4.5 per cent sodium chloride); later, it may be followed by a more appropriate solution as the clinical and laboratory findings will warrant.

Adjustment of Acid-Base Equilibrium.—If acidosis of nonketogenic type is present (*hyperpnea* and *highly acid urine*), salt solution alone will not relieve the condition. Sodium should be supplied in the form of bicarbonate or lactate. There are serious technical difficulties in preparing sterile solutions of sodium bicarbonate for intravenous use. If it is boiled or autoclaved in an unsealed vessel, it is decomposed into a highly toxic sodium carbonate. Because of these limitations *sodium lactate* is used. It yields in the body its sodium ion to form soda bicarbonate at a sufficiently rapid rate to supply alkali as needed and yet not so rapidly as to produce uncompensated alkalosis. Molar sodium lactate may be procured in sterilized ampoules of 40 cc. and, when diluted with 200 cc. of sterile distilled water (five times), it makes a one-sixth molar sodium lactate which is practically an isotonic solution. In severe acidosis (diabetic) Hartmann recommended to use 60 cc. of the diluted isotonic solution per kg. of body weight; one half of this amount is given intravenously and one half subcutaneously. The subsequent administration of fluids should consist of Ringer's solution or saline, 40 cc. per kg. of body weight.

Ringer's solution contains the chlorides of sodium, potassium and calcium and may be used instead of saline solution. *Hartmann's solution* is a combination of Ringer's solution and sodium lactate. It contains less chloride than the blood, and therefore will not increase acidosis. In case it is not possible to make blood chemical analyses, Hartmann's solution will correct either acidosis or alkalosis without danger of increasing either.

When the chlorides of the blood are above normal, the administration of an isotonic salt solution (0.9 per cent) may further replace the bicarbonates and increase the acidosis,

especially when the output of urine is decreased. In such instances, Ringer's or Hartmann's solution is preferable. In ketogenic acidosis, sodium lactate solution or dextrose is indicated and it may be supplemented with insulin. Five per cent dextrose given intravenously at a moderate rate is removed from the blood stream as rapidly as it enters and is metabolized in the usual way. If the rate is rapid or a 10 or 20 per cent solution is given, it is not fully metabolized and a certain amount of dextrose will spill over through the kidneys. In this manner, the concentrated dextrose solution produces a degree of diuresis and dehydration and thus we defeat our purpose. By giving dextrose a certain amount of nourishment is supplied; however, the caloric value is comparatively small, *e. g.*, 3000 cc. of 5 per cent dextrose will furnish only 600 calories. It is to be borne in mind that glucose, when given subcutaneously to patients with a salt deficit, will immobilize the already depleted stores of sodium and chloride. In the acute crisis of Addison's disease, it is best to administer intravenously copious amounts of a solution composed of 10 per cent dextrose, 1 per cent sodium chloride, and 0.5 per cent sodium citrate.

Alkalosis.—In severe alkalosis, normal saline may at times fail to correct the electrolyte disturbance. Under these circumstances, a 5 per cent isotonic dextrose in distilled water is given and the chlorides are supplied by means of ammonium chloride, calcium chloride, or even hydrochloric acid.

Untoward Reactions.—It is to be emphasized that salt in the tissues, unlike dextrose, is not metabolized, and therefore excessive use of salt solution in patients with a normal blood chloride level may result in edema in dependent portions of the body or in a vital organ, *e. g.*, brain, and irritative cerebral phenomena may become manifest.

Shock.—The administration of saline or dextrose may temporarily ameliorate shock; however, because of their great diffusibility they are insufficient to maintain blood volume or blood pressure. *Transfusion* of whole blood or blood plasma should be given without delay. According to Strumia, the intravenous use of *citrated blood plasma* is an ideal means for rapid relief of clinical symptoms of secondary shock.

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CLINIC OF DR. ALEXANDER STERLING

FROM THE ALLERGY DEPARTMENT OF THE NORTHERN LIBERTIES HOSPITAL BY GRANT OF THE SIMELSON POST, WAR VETERANS OF PHILADELPHIA

DANGERS ATTENDING THE CLINICAL USE OF EPINEPHRINE IN BRONCHIAL ASTHMA

EPINEPHRINE is specific in the relief of bronchial asthma. It can be used *subcutaneously, intramuscularly, intravenously* and by *inhalation*.

Allergists have indicated the proper dosage of epinephrine for various allergic manifestations, but a number of physicians still use *too large a dose*. One or two minims is all that is necessary to relieve any acute allergic manifestation, such as an attack of bronchial asthma, angioneurotic edema, pruritus, urticaria or serum reactions. When the patient is not improved within a half hour, another dose of 1 or 2 minims of epinephrine should be given then.

Clinical Effects of Epinephrine.—The clinical effects of epinephrine in the human can be divided into three stages:

1. The stage of *normal physiologic reaction*. One to two minims produces pallor, slight tremor, and palpitation (which indicate to the physician that the drug has been absorbed). There is relief from wheezing and dyspnea in the case of bronchial asthma, and the easing of symptoms in other allergic syndromes.

2. The stage of *alarm reaction*. When an overdose (0.5 to 1 cc.) of epinephrine is given to a normal patient, or when a small dose (1 to 3 minims) is given to a patient who is hypersusceptible, the physiologic effects are markedly exaggerated. Alarming symptoms may take place: extreme nervousness, precordial pain and distress, tachycardia (130 to 140), profuse perspiration and rise in temperature. Recovery follows in from one half to one hour.

3. The stage of *toxic reaction*. An overdose of epinephrine, or a physiologic dose in a susceptible patient, can produce toxic manifestations. Symptoms of normal reaction are followed very rapidly by symptoms of alarm reaction, and these progress to: (a) acute pulmonary edema (recovery possible); (b) acute cardiac dilatation (recovery possible); (c) acute ventricular fibrillation (recovery not common).

Toxic Manifestations.—Toxic manifestations to the clinical use of epinephrine can appear whether it is administered

subcutaneously, intravenously in saline, intramuscularly in oil, or inhaled through an atomizer by the patient.

Epinephrine *increases the cardiac rate* to such an extreme that it decreases the efficiency of the contractility of the heart, prevents complete emptying of the heart, and results in backing up the circulation; hence, pulmonary edema and liver shock. Epinephrine also produces capillary and venous stasis, with collapse and emptying of the small arterioles, resulting directly or indirectly in edema of the lungs.

Epinephrine in larger quantities can produce *prostration, collapse and paralysis of central nervous system*, terminating in failure of respiration and edema of lungs. (Cushny; p. 394; Lea and Febiger.)

One must be on guard when using epinephrine in cases of *hyperthyroidism*, in cases of *cardiovascular diseases with cardiac dilatation*, and in cases of *angina* with or without evidence of coronary thrombosis, because in such cases the pharmacologic effect of the drug may be disastrous.

SUMMARY

The *normal dose* of epinephrine is from 2 to 3 minims repeated every two or three hours for several doses until not more than 1 cc. is given in twenty-four hours. Overdosage occurs if 0.5 to 1 cc. is given in one injection. Toxic reactions may occur either to a normal dose in susceptible individuals or to a large dose in normal individuals.

Idiosyncrasies to epinephrine and the oncoming toxic effects are not recognized as such because they are usually mistaken for an increase in the bronchial asthma syndrome. The differential diagnosis between *acute bronchial asthma* and *epinephrine toxicity* must be kept in mind (Table 1).

TABLE 1

COMPARATIVE EFFECTS AND DIFFERENTIAL DIAGNOSIS OF EPINEPHRINE TOXICITY AND ACUTE BRONCHIAL ASTHMA

<i>Symptoms.</i>	<i>Bronchial Asthma.</i>	<i>Epinephrine Toxicity.</i>
Wheezing.....	Present.	Very little.
Dyspnea.....	Present.	Present.
Pallor.....	Present.	Very extreme—ashen gray.
Anxiety.....	Some.	Very severe.
Cold, clammy skin.....	Not present.	Present.
Heart rate.....	80-110 (usual).	130-180 (usual).
Palpitation.....	Some.	Extreme.
Precordial or mediastinal pain.....	None.	Very severe.
Fainting.....	None.	Present.
Weakness.....	Some.	Extreme.
Fatality.....	Rare.	Possible.

ILLUSTRATIVE CASES

Case I.—F. N., a female, two years old, seen August 17, 1939 (referred by Dr. Jacob Glauser) because of severe bronchial asthma one year's duration.

Spontaneous, normal birth.

At five months of age, this child developed hives when weaned. At eleven months she began to develop sneezing, rhinitis, and bronchial asthma. These attacks did not respond to treatment at home or in the hospital. In March, 1939, she had bronchopneumonia. After her recovery, she was taken to the country; she felt well for the first week and then relapsed into severe bronchial asthma.

The patient was seen in August, 1939, at the age of two. She showed no cutaneous sensitivity. She improved, however, on mild sedative and salicylates.

About two weeks later, the baby was brought to the office with a severe attack of bronchial asthma. The pulse and temperature were normal, but there was extreme dyspnea and wheezing. Two minims of epinephrine were given and the patient was kept for observation. In half an hour the child was neither better nor worse. Another 2 minims of epinephrine were given. After an hour the patient's dyspnea was worse. Another 3 minims of epinephrine were then given (so that, in the course of about two hours, 7 minims of epinephrine were administered). The difficulty in breathing became very much more pronounced; marked cyanosis was present in the lips and fingernail beds. The temperature rose to 102.5° F., and there were signs of pulmonary edema. The child was sent to the hospital and placed in an oxygen tent. Upon admission to the hospital, her temperature had risen to 103.5° F. The patient was watched very closely and instructions were given not to administer any epinephrine. Very small doses of atropine sulfate and digitalis were given. In the morning she was improved; her temperature was normal, and the pulmonary edema, cyanosis and all other symptoms had cleared.

This case illustrates the toxic effect of epinephrine on the cardiovascular system, producing pulmonary edema, in a hypersusceptible patient. This patient will not improve as long as epinephrine is used to relieve the asthmatic attacks.

The physician must therefore be *constantly on the watch*. If he treats a patient and there is no epinephrine response, other measures should be resorted to instead of persevering in the administration of epinephrine.

Case II.—M. G., male, aged thirty-one, a carpenter, was seen April 14, 1939, because of bronchial asthma of three days' duration, unrelieved by any medication.

In April, 1934, working in subway excavation as a carpenter, he suffered from severe coughing spells and headaches which became progressively worse; this was followed by attacks of bronchial asthma. He was hospitalized, nasal polyps and adenoids were removed, and operations on his sinuses were done, with very little improvement. By the end of 1934 he was having from three to fifteen attacks of bronchial asthma a day, each lasting from one half to four hours. Epinephrine was used for these attacks, but with no relief. He lost 61 pounds in seven months, down to 125 pounds.

Many hospitalizations in Philadelphia did not help. In 1934 he left for the west. He stayed in Texas, Arizona, New Mexico and Mexico. He worked

as a cowhand and as a carpenter. His condition remained about the same, although at times he felt somewhat improved.

On his return to Philadelphia in 1937, he continued to have severe attacks of bronchial asthma. He gave himself about twenty injections of epinephrine a day, consuming about 1 ounce. His condition became so bad that he was taken to the hospital in an ambulance, where he was treated for five weeks without relief. At another hospital, he was given five blood transfusions and also had bronchoscopic treatments. He was sent home in six weeks with no improvement. He began to realize that epinephrine injections were not giving him any relief, although he continued to use the epinephrine subcutaneously and in a spray (1:100) which gave him occasional relief.

From all these years spent in hospitals he learned that he was highly sensitive to many drugs. When he took certain drugs he went into severe attacks of status asthmaticus or shock; and on many occasions he had to fight for his life. He was sensitive to aspirin, caffeine, belladonna, iodides, digitalis, ephedrine, argyrol and salt solution washings for his nose. He does not know of ever having had any food sensitivity.

Attacks are severe day or night, summer or winter, although he thinks that in the winter they are much worse. On windy and rainy days he feels somewhat better; on windy and sunny days his attacks are aggravated. (The molds from various carpentry work in old and damp houses will dry up and spread very easily in windy and sunny weather, but they spread very little in rainy weather, which may be the explanation here.)

With this history, the patient was ushered into my office with the help of two people. He was sent to the hospital, where he was placed in a helium and oxygen tent. He was relieved in the course of one-half hour and went home. He was informed of the uselessness of epinephrine injections.

Two or three days later, he called at the office again in a very severe attack of bronchial asthma. He had taken a large number of epinephrine injections as well as inhalations that day. His dyspnea and pain in the chest was extreme and he begged for help.

An opportunity to demonstrate epinephrine toxicity in an epinephrine-fast patient presented itself. He was therefore given 3 minims of epinephrine by hypodermic and was asked to wait. Forty-five minutes later his condition was just the same. Another 3 minims of epinephrine was administered. Forty-five minutes later, his condition was much worse and another 3 minims of epinephrine was given. After the third injection his condition became so alarming and his dyspnea and pain in the chest (no angina, no precordial pain) so much more severe that his family was called to take him to the hospital.

The strain on the right side of the heart, produced by the repeated epinephrine medication, was immediately relieved by bleeding; the dyspnea and general chest pain disappeared. In two hours he was well enough to go home.

Even after this episode, however, the patient would not abstain from epinephrine injections or inhalations and, three days later, was again admitted to the hospital. Epinephrine medication was gradually stopped. The patient was well so long as he stayed away from epinephrine the remainder of the three weeks' stay in the hospital.

This case illustrates cardiac dilatation due to large amounts of epinephrine which was relieved by relieving the strain on the right heart. Epinephrine did not help this patient's asthma; it only increased his symptoms.

Case III.—B. W., male, thirty-two years old. Seen February 3, 1936, because of bronchial asthma of four years' duration.

This patient was sensitive to bacteria, food and inhalants. From 1936 to 1938 he was treated for dust, and by bacterial vaccines and elimination of positive food factors. Three minims of epinephrine gave no relief but made symptoms worse. April 14, 1938, he was admitted to the hospital because of status asthmaticus. He was relieved by phenobarbital, aminophyllin and salicylates. He had acute asthma in January, 1938, and epinephrine produced an increase in symptoms. A second dose, given within one-half hour, produced partial unconsciousness. For further relief, he was put in an oxygen tent and given aminophyllin.

This case illustrates secondary inflammatory changes plus a sensitivity to epinephrine. Care in treatment includes not giving epinephrine for acute attacks and mild sedative symptomatic treatment.

Case IV.—R. P., female, fifty-three years of age, seen August 1, 1931, because of bronchial asthma.

This patient was sensitive to inhalants, food, and bacteria, and was under treatment with house dust and autogenous vaccine. She was unable to take epinephrine in doses of more than 1 minim.

In March, 1938, she required radium for a uterine neoplasm. She developed attacks of bronchial asthma, unrelieved by epinephrine. Her symptoms increased. The symptoms were finally relieved by discontinuing epinephrine and using sedatives and salicylates.

Cases III and IV show an increase of the asthmatic syndrome on use of epinephrine because of sensitivity.

Case V.—R. P., female, thirty-three years old, seen April 14, 1938, because of bronchial asthma of four to six months' duration.

Five minims of epinephrine produced acute shock, requiring digalen, caffeine and other energetic stimulations.

Case VI.—M. P., female, aged thirty-nine, seen August, 1933, because of bronchial asthma of ten years' duration.

One to two minims of epinephrine produced shock.

Cases V and VI illustrate patients in whom epinephrine in small doses produced shock.

Case VII.—M. P., male, aged forty-three, was brought to my office February 20, 1940, because of shock.

He had purchased epinephrine for use as spray to control his bronchial asthma. After having used large amounts previously that day, the additional amount sprayed into his throat at the drug store was sufficient to produce shock.

Case VIII.—R. F., female, forty-six, referred because of bronchial asthma, urticaria and angioneurotic edema of three days' duration.

This patient had been given 8 injections of epinephrine in twenty-four hours. The last two injections were 10 minims and six minims each. The doctor called on me to help relieve the patient of what he thought was an acute attack of bronchial asthma, presenting dyspnea and extreme presternal chest pains. Examination showed that the patient had imperceptible irregular cardiac function. Her skin was ashen-gray. There was no wheezing. The diagnosis of epinephrine overdosage was made. The patient was put to bed and given phenobarbital. She felt improved in an hour. Against advice, she left her home to visit her parents. When she arrived at her parents' home, she expired.

This case illustrates a fatality undoubtedly due to epinephrine overdosage. The symptoms were similar to those of severe attacks of bronchial asthma, but sufficient differential points were present to indicate that epinephrine overdosage was present.

CONCLUSIONS

1. The usual therapeutic dosage of epinephrine (0.5 to 1 cc. of a 1:1000 solution) is dangerous, and more especially if repeated when it has not relieved symptoms.
2. Maximal therapeutic effects can be obtained by a dose of 0.10 to 0.15 cc. repeated at intervals of thirty minutes for two or three doses if necessary.
3. The therapeutic dosage can in certain cases produce a fatality.
4. The symptoms of epinephrine toxicity must be differentiated from those of acute bronchial asthma.

CLINIC OF DRS. MARIO A. CASTALLO AND LOUIS G. FEO

FROM THE DEPARTMENT OF OBSTETRICS, JEFFERSON MEDICAL
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THE ROLE OF ANTENATAL VAGINAL ANTISEPSIS IN THE PREVENTION OF OPHTHALMIA NEONATORUM*

THE efficacy of the usual routine employed for the prevention of ophthalmia neonatorum has been taken so much for granted that some of the fundamental principles have been forgotten. It recently has been shown that in one of our largest cities the incidence of gonorrheal ophthalmia in the newborn is about *twenty-two times greater* now than during the time immediately following Credé's monumental work over a hundred years ago.

It will therefore be the purpose of this clinic once more to call attention to the importance of the first principles established on this subject, and to review our personal experiences in the prevention of gonorrheal ophthalmia during the past ten years.

It is estimated that *twenty* out of every *hundred* blind persons owe their infirmity to a gonorrheal infection in their mothers. In spite of prophylactic methods known to the public and the therapeusis of the disease, the incidence of gonococcal infections in married women is still very high. Gonorrhea causes much more infirmity in women than does syphilis, and directly causes much damage to the children born of infected patients. It is therefore just as important to include *cervical* and *urethral smears* as part of the prenatal examination as it is to obtain blood for a Wassermann test. Laws have been enacted in some states to ascertain the presence of a syphilitic infection as part of the premarital examination (before a marriage license is issued). Obviously the law is incomplete in its purpose if it does not ascertain the presence or absence of the equally important gonorrheal infection.

* We wish to acknowledge with thanks the generosity of Drs. P. Brooke Bland and Norris W. Vaux in granting us the facilities of the clinic.

The best form of treatment is of course *prevention*. Few similar opportunities are offered physicians in the realm of preventive medicine than in the combating of ophthalmia neonatorum. The local infection in a pregnant woman is completely separated from the unborn child until the membranes are ruptured. We therefore have many months, usually, and at least weeks, at our disposal to treat the disease before the newborn child's eyes come in contact with the infected vaginal secretions.

History.—Inflammation of the eyes of the newborn was recognized by Soranus and Aetius who in the very earliest days of medicine referred to ophthalmia neonatorum.¹³ Tuelinoz as early as 1750 believed that leukorrhea in the mother was the cause of the malady.¹⁴ Gibson² in 1807 established certain principles for the prevention of the sore eyes which occurred in newborn infants. He advocated the following procedures:

1. To remove, if possible, the disease in the mother during pregnancy.
2. To remove as much of the discharge as possible at the time of delivery.
3. To wash the baby's eyes with a liquid calculated to remove the offending matter, or to prevent its activity.

The suggestions of Gibson were overshadowed by Credé's definite teachings which appeared eighty years later. Credé's first efforts were to clean the vagina. He employed irrigations of lukewarm water or weak carbolic acid solution.⁷ Following this procedure the eye infections were less frequent, but still this therapy did not give very satisfactory results. Credé then directed his study to the prophylactic disinfection of the infant's eyes. His experiments with a mild boric acid solution were successful, provided the infected mothers had been carefully treated with vaginal irrigations throughout the entire labor. This form of therapy was discontinued when it was found that a 2 per cent solution of silver nitrate applied in a single drop from a glass rod onto the conjunctiva gave striking results. Credé then concluded that the *disinfection of the child's eyes*, and not that of the mother's vagina, was of paramount importance. Thereupon the instillation of the silver solution alone as a proper method of prophylaxis found universal favor.

Definition.—The term "ophthalmia neonatorum" is usually applied to that more serious group of eye infections due to the gonococcus. The reported percentages of ophthalmia

attributed to the gonococcus is high (30 to above 50 per cent^{10, 20}); the remaining infections are due to various other organisms: the pneumococcus, *B. coli*, staphylococci, streptococci, and inclusion bodies.²² Thygeson⁴ reported 0.022 per cent of ophthalmia due to the gonococcus in his series of 3939 newborn infants and 6.6 per cent of nongonococcal ophthalmia. In our series 0.54 per cent of the babies had non-specific ophthalmia (Table 1). When reporting percentages or when comparing statistical surveys it is important to distinguish between the two forms. In the light of the fact that

TABLE 1

Year.	Patients delivered.	Incidence of gonorrhea.	Incidence of gonorrheal ophthalmia.			Nonspecific ophthalmia.
			Among treated mothers.	Among nontreated mothers.	Among nondiagnosed mothers.	
1928	675	7	0	0	5	0
1929	653	9	0	0	5	0
1930	697	16	0	0	3	0
1931	700	5	0	0	0	0
1932	861	47	0	0	2	8
1933	851	35	0	0	0	6
1934	739	25	0	3	0	1
1935	624	8	0	0	2	4
1936	644	11	0	0	0	2
1937	672	37	0	1	1	3
Totals	7,116	200	0	4*	18	24

* 1. Smears not taken; no treatment.

1. Refused treatment.

1. Registered two days before delivery.

1. Received only one treatment.

Credé's technic, as shown by Thygeson,⁴ failed to protect against the nongonococcal form, it becomes absolutely necessary to make this distinction.

Incidence.—The frequency of gonorrhea in relation to pregnancy, according to European writers, varies from 1.5 to 50 per cent.¹⁴ American series show a generally lower incidence of infection, averaging from 5 to 10 per cent of pregnant patients.¹⁴ This wide variation is due to a number of factors: Gonorrhea in pregnancy varies according to the author and his class of patients, and most important, accord-

ing to the method employed in diagnosis. This latter factor was clearly demonstrated by Sorrentino,⁸ who found in a total of 21,475 pregnancies over a period of four years (1931-5) 174 cases of gonorrhea; yet when a trained personnel was entrusted with the diagnosis, there was found seventy cases in a one-year period (1934-5), as compared to 104 for the previous years.

In the In-patient service of the Jefferson Medical College Hospital, 7,116 deliveries were recorded from 1928 to 1937, inclusive. In this group 200 mothers were found to have gonorrhea, and 18 additional mothers, while diagnosed negative for the disease antenatally, gave birth to infants who developed ophthalmia neonatorum, or an incidence of 3 per cent (Table 2).

TABLE 2

INCIDENCE

Gonorrhea.	Ophthalmia neonatorum, nontreated mothers.	Ophthalmia neonatorum, treated mothers.	Nonspecific ophthalmia neonatorum.	Morbidity in gonorrheal patients.
3.0 per cent.	0.31 per cent.	0 per cent.	0.54 per cent.	7.0 per cent.

Contrasted with the maintained high percentage of gonorrhea complicating pregnancy, ophthalmia neonatorum has shown an epocal drop with the introduction of the Credé technic. The first phenomenal drop was shown by him at the University Clinic and Polyclinic for Obstetrics and Gynecology and School for Mid-Wives at Leipzig. Before the routine use of silver nitrate at this institution, 10.8 per cent of 2897 babies born had gonorrheal ophthalmia. Following its use about 0.15 per cent of 1160 babies developed the disease, the highest figure recorded in any one year being 0.49 per cent.⁴ Other reports throughout the civilized world soon followed, showing a marked decline in ophthalmia with the employment of the Credé technic. The Los Angeles Hospital,³ whose procedure after wiping the eyes with dry cotton was to use 2 drops of a 1 per cent solution of silver nitrate, reported 0.22 per cent of cases of ophthalmia neonatorum. In our group, ophthalmia neonatorum did not occur in babies born of treated infected patients, but 0.31 per cent of babies born of untreated mothers developed the disease (Table 2).

Soon after the discovery of the gonococcus by Neisser, Haussmann⁷ in 1882 said, "Now that the cause of ophthalmia neonatorum is known may it soon, through the co-operation of all, become extinguished and be classed with the diseases of only historical interest." The brilliant results published by authors immediately after the introduction of Credé's technic would tend to bear this out. But today, in retrospect, Haussmann's wish is not fulfilled. Marshall,⁸ for example, has shown that, after fifty years of silver nitrate prophylaxis, gonorrhea still accounts for 20 per cent of all blindness in state institutions.

Lehrfeld⁹ found in 1935 that, during the preceding fifteen years, 2.2 per cent of 27,873 infants born in Philadelphia developed ophthalmia, which makes it 22 times more prevalent than in Credé's era.

Although the silver nitrate may be at fault, or the technic as employed today may be inefficient, nevertheless statistics show that the use of the silver salt alone does not offer sufficient protection. Whether the generally used 1 per cent solution of silver nitrate instead of the original 2 per cent solution is the only factor, it is difficult to state. The experiment of Gottlieb and Freeman⁵ shows that a 1 per cent preparation of silver nitrate in the presence of physiologic saline cannot be depended upon to inhibit the growth of the gonococcus organism *in vitro*. Cognizant of this apparent irreducible minimal incidence, subsequent workers^{12, 20, 21, 14, 15} have emphasized special prenatal supervision of the pregnant woman infected with gonorrhea. Whether this takes the form of actual treatment of the infection, or prophylactic medication, in view of reducing ophthalmia, the pendulum is swinging back to the principles first advised by Gibson and re-enforced by Credé's discovery.

Diagnosis.—The diagnosis of gonorrhea in women is not always easy, and during pregnancy the same difficulties are present. A greater number of cases will be diagnosed if, in addition to obtaining *smears*, the *history* and *clinical findings* are carefully evaluated. Urethral and cervical smears should be taken on every pregnant woman, for it is in these regions that the gonococci find a habitat. Not only should the smears be taken at the *beginning* of pregnancy, but they should be repeated between the *seventh* and *eighth month* of gestation. It is an all too common occurrence in our wards that a woman who has negative smears at the beginning of her pregnancy, will deliver a baby that will develop ophthalmia neonatorum

due to a gonorrheal infection which the patient has acquired a few weeks or months prior to her delivery. It is common knowledge also that pregnancy may cause an acute exacerbation of a latent infection; therefore, often repeated microscopic studies should be made, a fact which is stressed by many workers.^{16, 3, 6, 15}

There are many pitfalls in the *microscopic diagnosis* of gonorrhea, but a negative smear in the presence of the well-known clinical picture should not deter one from the institution of treatment in any pregnant woman. A moderate to profuse yellow, or greenish-yellow, creamy, foul-smelling discharge, smarting on urination, irritated urethra and inflamed vagina have been our *criteria for treatment* whether or not the laboratory reports the presence of intracellular gram-negative diplococci, excluding the possibility of monilia and trichomonas infestations.

All patients admitted to the antenatal clinic are given a *routine physical* and *obstetrical examination* at the first visit, and smears (urethral, vaginal and cervical) are taken. These are re-checked eight to ten weeks prior to the estimated date of delivery. All patients who give a history of having had a purulent discharge or who are found to harbor gonococci, and others who show a clinical picture of gonorrhea even though the microscopic examination is negative, are referred to the special clinic for treatment.

TREATMENT

The treatment of gonorrhea in pregnancy differs very little from that in the nonpregnant woman except in its intensity and the relative weakness of the solutions employed. The newer nonirritating antiseptic solutions lend themselves very well to this form of treatment. Among the many may be mentioned aqueous *merthiolate*, *metaphen* and *mercurochrome*.

Gonorrhea in most cases is a self-limited disease and all that one may expect to do during the time available is to keep the parts as clean as possible, and allow the patient's own resistant powers an opportunity to overcome the infection.

In the obstetrical clinic of the Jefferson Medical College Hospital, systematic treatment of gonorrhea during pregnancy has been followed since 1926. This includes local vaginal medication throughout pregnancy—a mode of therapy not since the inception of this clinic, or now, generally practiced. Since instituting antenatal vaginal antiseptics no instance of ophthalmia neonatorum has occurred among the 170 women

adequately treated antenatally for gonorrhea. One case of ophthalmia neonatorum occurred in a patient who had only one vaginal treatment prior to her delivery. During the same period of time there have occurred twenty-one cases of ophthalmia neonatorum, all in patients who either were brought into the hospital during labor and who refused to come for treatment, or who were not suspected of having gonorrhea, and who therefore were not treated during pregnancy (Table 1).

The treatment employed in this clinic is divided into three definite parts:

1. *Clinic treatment.*
2. *Treatment which is to be carried out at home.*
3. *Treatment of the baby's eyes after birth.*

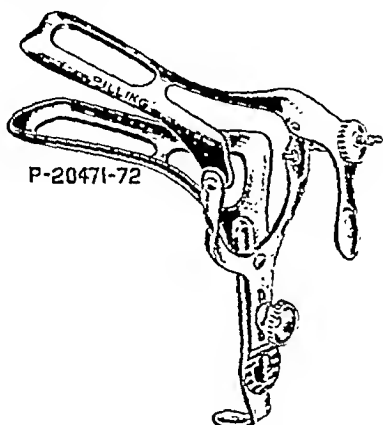


Fig. 215.—Feo's fenestrated speculum.

1. **Clinic Treatment.**—With the patient in the lithotomy position the vagina is exposed with a speculum, preferably of the bivalved type (Feo) (Fig. 215). This instrument simultaneously exposes the urethra, cervix and a maximum amount of vaginal surface. With practice it may be used with ease and little discomfort to the patient. The secretions of the vagina, cervix and about the urethra are then swabbed out by means of cotton sponges impregnated with liquor antisepticus solution. The excess is then removed with dry cotton absorbent sponges and the parts are painted with aqueous 1:1000 metaphen solution. Cotton applicators saturated with metaphen are then placed in the urethra and cervix. These are allowed to remain for a short length of time. Large cotton

sponges should be used throughout to minimize pain and traumatization of the inflamed surfaces. Gentleness is practiced constantly. The patient is requested to report for weekly treatment until labor intervenes.

The patient is instructed as to the infectiousness of the discharge and the necessity of scrupulous washing of the hands and complete segregation of toilet articles. The husband of the patient should be referred for diagnosis and possible treatment.

2. **Home Treatment.**—Home treatment consists of a daily douche with Lugol's solution, 1 teaspoonful to 2 quarts of water. The instructions are as follows: A 2-gallon covered receptacle filled with water into which the douche bag and nozzle are placed is allowed to boil for twenty minutes, at the end of which time this utensil is allowed to cool. The patient is then instructed to use this sterilized bag and solution. To the water is added the Lugol preparation. The patient is instructed to wash the genitalia with soap and water and take the douche in a lying-down position with the bag never more than 1 foot above the level of the hips. It is stressed that a glass rounded-end nozzle with eccentric openings be employed. This should never be inserted further than 1 inch beyond the bulbous end.

3. **Treatment of the Baby's Eyes after Birth.**—It is our conviction that the eyes of the newborn should be flushed out with boric acid immediately upon delivery and that this should be followed by the instillation of several drops of 1 per cent silver nitrate. The silver solution is allowed to remain in the eyes of the infant until the cord is dressed and the baby prepared for its transference into its warm bassinet, and then the eyes are flushed out with the normal saline.

Note: We believe that in every instance of infected mothers it is most important that their newborn babies' eyes be treated more vigorously. These children should have instilled into their eyes on the three successive days following delivery, 0.5 per cent silver nitrate. This solution is allowed to remain without subsequent flushing out. This form of treatment will occasionally produce slight conjunctival irritation, but if fresh preparations are employed and care is exercised in the instillation, preferably with the metal retractors (Fig. 216), this slight irritation will be rarely encountered.

A word of caution: It does not happen very frequently, but on occasion drugs other than silver nitrate have been inadvertently instilled into the eyes of a newborn baby. One should always write in longhand the *percentage* of solution re-

quested, *not the numerals*, and invariably see to it personally that the prescription is freshly mixed and properly labeled. We know of one instance where 10 per cent silver nitrate was instilled and in another where carbolic acid was used—needless to say with grave disaster.

A point which is not completely appreciated is the fact that if the silver nitrate solution is not instilled into the baby's eyes *directly*, naturally its efficacy is lost. It is not an easy

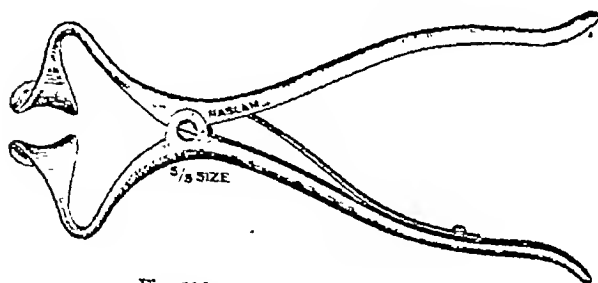


Fig. 216.—Castallo's eyelid retractor.

task at times, with rubber-gloved hands on which there is a goodly amount of vernix caseosa, to open the baby's eyelids sufficiently to instill the medication. One of us (C.) has devised an eyelid retractor which fits on the outer aspect of the eyelids and employs the palpebral cartilage as an impinging point to open the eyelids without trauma (Fig. 216).¹¹

Recent Developments.—Sulfanilamide and its newer derivatives have been employed recently for the treatment of gonorrhea. A voluminous literature has accumulated. Bomze,

Fuerstuer and Falls¹ report a group of nineteen pregnant women infected with gonorrhea among a series of forty-five women with gonorrheal infection. Fifty-seven per cent of the patients developed toxic manifestations. The dosage employed was 40 grains daily in five-day courses. The writers claim cure was accomplished in all cases except one. Reinfection occurred fourteen times in their series. Of these, all but one admitted re-exposure with the same partners who had originally infected them.

The series reported above is too small, as the authors themselves state, to draw any definite conclusions. On the strength of this study and other good reports on the treatment of gonorrhea with the sulfanilamide group, we are cautiously conducting a study in patients who are pregnant, as a check-up on our usual mode of management.

It is concluded from studies made at Johns Hopkins Hospital that, until the effects of sulfanilamide on the human fetus are better known, the drug should be administered with extreme caution during pregnancy.

Using rats in carefully controlled experiments, Harold Speert²³ has recently reported that prolonged administration of sulfanilamide to pregnant rats produces deleterious effects in the offspring, including increased intra-uterine death and small litter size, diminished birth weight and selective stunting of growth.

Silver acetate has found a place in the prevention of ophthalmia neonatorum. It has found favor because it will not go into solution above 1.2 per cent and is said to be less irritating.¹⁷ A series reported by Hartman²⁴ shows that without antenatal antisepsis the protection afforded the infant is about on a par with that obtained with silver nitrate.

Argyrol, because of its less irritating properties, is another drug which has been employed instead of silver nitrate. Douglas and Stone¹⁸ were employing 5 per cent argyrol instillations into the newborn babies' eyes when an epidemic occurred. This was checked when 1 per cent silver nitrate was substituted.

Results.—In infants born of the 200 maternal patients in our series there occurred four cases of ophthalmia. But in none of these four instances did the mother receive adequate antenatal vaginal antisepsis. One case of gonorrheal ophthalmia developed in the infant of an infected mother who received only one antenatal treatment, and whose pregnancy was complicated by a ruptured Bartholin cyst; another in the infant of

an infected mother who refused prenatal medication, and one in an infant whose mother registered in the clinic only two days before delivery. The fourth case was one in which the routine smears were not taken in the mother and, therefore, she was not referred for treatment (Table 1).

The four cases of ophthalmia, above mentioned, are to be added to the eighteen others which developed in the infants of patients who were diagnosed antenatally negative for gonorrhea, and consequently received no vaginal antisepsis. The eighteen occurrences of ophthalmia neonatorum resulted in spite of the routinely applied prophylaxis of Credé (Table 1). This study also revealed, with due credit to the Credé method, twenty-six cases of gonorrhea-positive mothers who escaped treatment and whose babies did not develop ophthalmia. The incidence of ophthalmia neonatorum has been reduced in treated cases to zero, at the Jefferson Medical College Hospital, by combining antenatal vaginal antisepsis with the more generally accepted method of prophylaxis (Table 2).

The efficacy of antenatal treatment was further illustrated by a study made in Philadelphia to find the reason for the high incidence of ophthalmia in the city.⁶ Records of six large institutions were examined and two hospitals were found to have an incidence one fifth that of the others. In both these hospitals, the Jefferson Hospital and the Philadelphia General Hospital, the clinics are run along the same therapeutic lines.

Morbidity.—The routine applications of the method of treatment advocated has had no harmful effects on the normal progress of pregnancy. In our series there occurred but one abortion and ten premature births (Table 3). There were

TABLE 3

Year.	Cases of gonorrhea.	Abortions in gonorrheal patients.	Premature births in gonorrheal patients.	Morbid patients.
1928 to 1937	200	1	10	26*

* The morbidity in 14 mothers is unaccounted for except for possible gonorrheal infection.

twenty-six infected patients, a morbidity of 7 per cent; fourteen in which the cause is unaccounted for; while the morbidity rate for the clinic as a whole is 17 to 25 per cent.

SUMMARY AND CONCLUSIONS

1. A total of 218 maternal cases of gonorrhea were observed among 7,116 deliveries, an incidence of 3 per cent.

2. Of 200 patients in whom the diagnosis was made antenatally, 170 received adequate local treatment during pregnancy. In the infants of these mothers no instance of ophthalmia neonatorum occurred.

3. Ophthalmia neonatorum occurred in twenty-two infants among the 7,116 deliveries, an incidence of 0.31 per cent. In eighteen instances the mothers were not treated because no evidence of gonorrhea was noted in the prenatal period. Of the remaining four mothers, one received only one treatment, one registered two days before delivery, another refused treatment and from a fourth smears were not obtained.

4. The puerperal morbidity among the 200 patients with known gonorrhea was 7 per cent. Abortion occurred in one patient, while ten had premature births.

The conclusion is, that prenatal treatment, together with careful instillation of silver nitrate, is not only safe but has proved to be a most efficacious means of preventing ophthalmia neonatorum.

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